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ORIGINAL ARTICLES

STUDIES ON THE ADMINISTRATION, ABSORPTION, DISTRIBUTION AND EXCRETION OF AUREOMYCIN IN CHILDREN

With Observations Concerning Tolerance, Dosage Schedules And Certain Therapeutic Indications

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AT A meeting of the New York Academy of Sciences in the summer of 1948 the discovery of a powerful new antibiotic, aureomycin, was announced. It was apparent from the laboratory data and preliminary clinical trials presented at that time[1] that aureomycin was destined to become an important clinical antibacterial agent. Its apparent advantages were that it could be administered orally, that it was of low toxicity, and that it was demonstrably active against certain rickettsiae and viruses, and against most pathogenic bacteria. Accordingly, a study of aureomycin was undertaken with the following purposes in mind: (1) to establish a rational dosage schedule for children (2) to collect data on the absorption, distribution, fate and excretion of aureomycin in children and (3) to subject the drug to cautious clinical trial as the opportunities presented themselves. This report is submitted at this time in hopes that the data will aid clinicians using aureomycin in children and investigators working in this field. Several studies covering part of the same ground in adults have been reported.[2-5] Local aureomycin therapy will not be considered here.

MATERIALS AND METHODS

The method of assay used in this study has been described.[6,7] The aureomycin was supplied as the hydrochloride by Lederle Laboratories Division of American Cyanamid Company, in 3 forms: (1) 50

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mg. vials, (2) 250 and 50 mg. capsules and (3) mixed with chocolate powder (aureomycin 50 mg./rounded teaspoon of powder). All 3 forms were used for oral administration, and aureomycin from the vials was used for parenteral administration. Aureomycin hydrochloride is a golden yellow crystalline powder which is soluble in water up to about 15 mg./100 cc. at 25°C., having a pH of about 3 in aqueous solution.[8] A diluent containing 26 mg. of l-leucine/100 cc. was also supplied by Lederle Laboratories for intravenous administration of aureomycin.

The children were hospitalized patients. Those used to assay aureomycin body fluid levels after single oral, intravenous and rectal doses of aureomycin were convalescing patients about to be discharged. Those whose body fluid aureomycin levels were assayed during a course of oral therapy were being treated with aureomycin for acute or chronic infections. All children studied had normal urinalyses and nothing in the history or physical examination suggesting impairment of renal function unless otherwise designated. All single doses of aureomycin were given by one of the authors. Patients on courses of aureomycin were given the drug by the ward medication nurse who was given special instructions for carrying out the order.

Results

1. Administration and Toxicity

A. Oral: Over 150 patients, ranging in age from newborn infants to adults, have been observed while receiving aureomycin in doses of approximately 44 to 66 mg./kg. body weight/day orally in courses lasting up to six weeks. The only evidence of toxicity or sensitivity observed occurred in three children whose skin apparently became hypersensitive to sunlight while they were receiving aureomycin. The one disturbing side effect has been the low tolerance of the gastrointestinal tract to aureomycin hydrochloride. The gastrointestinal symptoms, which seem directly related to the size of the oral dose, have been nausea, vomiting, generalized or epigastric abdominal pain and loose stools. Vomiting usually occurs only after several oral doses of aureomycin and is usually heralded by nausea and abdominal discomfort. In fact, 33 children who received a single oral dose of aureomycin 11 to 22 mg./kg. body weight had no gastrointestinal symptoms. Each individual has his own tolerance to aureomycin, but the clinical impression was that approximately 11 mg./kg. body weight given every four hours is the maximum amount which can conveniently be taken by most children without disturbing gastrointestinal symptoms. The incidence of vomiting among 48 children on such a dosage schedule has been 19% (nine instances). Three to four ounces of milk following each oral dose of the drug seems to increase the gastrointestinal tolerance. Aluminum hydroxide gel, as proposed by Bryer and co-workers,[9] has also been helpful in reducing the gastrointestinal symptoms in the few cases in which it was used.

The bitter taste of the drug makes difficult administration of aureomycin to children too small to take capsules. Chocolate milk (2 ounces of milk/50 mg. aureomycin chocolate powder), chocolate syrup (one dram/50 mg. aureomycin) and lemon syrup (one dram/50 mg. aureomycin) have been the most satisfactory vehicles. Coca-cola, corn syrup, honey, syrup of cherry (sweet and wild) and fruit preserves have been less satisfactory.

B. Intravenous: Aureomycin has been given intravenously to five children and one adult in doses of 2.2 mg./kg. body weight and to 7 children in doses of 6.6 mg./kg. body weight. In some cases the drug was given over a period of 15 minutes or more in 1/6 molar sodium lactate (aureomycin 0.5 to 1 mg./cc.), in which it has a pH of approximately 5; in other cases it was given rapidly in the l-leucine diluent (aureomycin 20 mg./cc. of diluent), in which it has a pH of about 8.2. The only untoward effects noted after intravenous administration were a bitter taste in the mouth and a dry tickling sensa-

tion in the trachea causing a cough for about 15 minutes after rapid intravenous injection of the larger dose. This could be largely overcome by taking two or more minutes to inject the drug.

C. Rectal: Four children and one of the authors have received rectal aureomycin in doses varying from approximately 6.6 to 15.4 mg./kg. body weight. It was given in perforated capsules following a cleansing enema. Intense rectal burning and discharge of the drug from the rectum within one hour after administration resulted in the four instances when one ounce of water was instilled after the aureomycin. Retention of the drug and no rectal burning resulted in the three instances when no water was instilled after the aureomycin. Comparable doses of aureomycin were used with and without the water instillation.

D. Intramuscular: Ten children have received the drug in repeated intramuscular doses of 2.2 to 5.5 mg./kg. body weight. Intense local pain and induration in all and febrile reactions in three resulted despite buffering of the drug and dilution in 0.5 to 1% procaine. No sloughs developed.

The drug was not given intrathecally.

TABLE 1

AUREOMYCIN SERUM CONCENTRATION AFTER SINGLE ORAL DOSE OF APPROXIMATELY 11 MG./KG. BODY WEIGHT

Patient	Wt. in kg.	Dose in mg.*	Serum Concentration in μg./cc.			
			1 hr.	4 hr.	6 hr.	8 hr.
M.T.	47.6	500	0.44	1.60	1.60	
D.F.	46.7	500	1.56	1.16	0.91	0.29
F.A.	40.8	500	0.88	2.30	2.40	
S.G.	36.3	500	0.32	0.98	1.40	<0.10
G.K.	36.3	500	<0.10	0.74	0.60	0.60
A.L.	32.2	350	0.26	1.28	1.35	1.42
R.M.	28.6	250	0.40	0.62	0.30	
J.Ma.	22.7	250	0.36	1.20	1.20	0.60
E.O.	22.2	250	0.25	1.40	1.05	0.66
J.B.	18.1	250	0.43	2.56	1.28	0.83
J.Jn.	24.5	240	<0.10	0.84	0.84	1.00
R.R.	16.3	150	0.38	0.76	0.94	
J.Mc.	15.0	150	1.20			
P.S.	14.5	150	0.90	2.00	1.36	
J.S.	11.3	100	0.34	0.51	0.72	
J.Js.	10.9	100	0.75	1.00		1.57
K.A.	9.1	100	0.48	0.60		
C.H.	8.2	100	0.90	1.00	1.76	
Range			<0.10–1.56	0.51–2.56	0.30–2.40	<0.10–1.57
Mean			0.55	1.21	1.17	0.79
Median			0.40	1.00	1.05	0.66

* Doses of 250 mg. and over given in capsule and followed by 3 to 4 oz. of milk.

Doses of <250 mg. given in chocolate milk, 2 oz./50 mg. of aureomycin, prepared from aureomycin mixed with chocolate powder.

Medication was given about 2 hr. after breakfast and about 1½ hr. before lunch.

2. Serum Levels with Various Routes of Administration

A. Oral: A single oral dose of aureomycin 11 mg./kg. body weight was given to 17 children, and serum levels were obtained 1, 4, 6 and 8 hours afterwards. The results are shown in table 1. Although there is considerable variation between patients, consistent findings are a slow attainment of peak levels, and maintenance of the peak levels for 4 to 8 hours after the administration of the antibiotic.

Twenty-two mg./kg. body weight was given in single doses to 10 children (table 2). No significant difference in serum levels or pattern of absorption occurred following this larger dose.

Serum aureomycin levels resulting during sustained therapy with 11 mg./kg. body

TABLE 2

AUREOMYCIN SERUM CONCENTRATION AFTER SINGLE ORAL DOSE OF 22 MG/KG. BODY WEIGHT*

Patient	Wt. in kg.	Dose in mg.	Serum Concentration in μg./cc.		
			1 hr.	4 hr.	8 hr.
B.M.	39.0	850	0.46	1.52	1.00
J.B.	18.1	400	0.87	1.47	0.62
M.H.	18.1	400	0.57	1.76	0.87
B.R.	27.2	600	0.20	2.00	0.85
L.A.	33.6	750	0.37	2.00	1.56
M.M	41.7	1000	0.48	1.08	0.50
L.E.	25.4	500	0.35	2.00	1.00
E.R.	33.1	750	0.31	0.65	0.39
S.H.	20.0	500	0.10	1.12	0.80
E.P.	30.4	750	0.50	1.20	0.61
Range			0.20–0.87	0.65–2.00	0.39–1.56
Mean			0.42	1.48	0.82
Median			0.42	1.50	0.83

* Medication given in capsules about 2 hr. after breakfast and 1½ hr. before lunch and followed by 4 oz. of milk.

weight every four hours are recorded in table 3. It will be noted that cumulation is inconstant and of a low order of magnitude. Usually, any cumulative effect appeared within 24 hours and did not increase thereafter. In table 4, serum levels obtained in a few children receiving 11 to 17.6 mg./kg. body weight every six hours are recorded. No significant difference is seen in these levels and those resulting from the four hour schedule.

B. Rectal: Serum levels obtained after rectal instillation of aureomycin approximately 6.6 to 15.4 mg./kg. body weight are shown in table 5. As has been mentioned, adequate retention of the drug in the rectum was impossible due to severe pain and irritation when the aureomycin was followed with water. The serum levels obtained are low.

C. Intramuscular: No precise data on the absorption of aureomycin after intramuscular administration was obtained, but the few serum levels run were very low.

D. Intravenous: Serum levels during 12 hour periods following the intravenous administration of aureomycin 6.6 mg./kg. body weight to seven children are shown in figure 1.

TABLE 3

SERUM, URINE AND SPINAL FLUID LEVELS DURING ORAL AUREOMYCIN THERAPY APPROXIMATELY 11 MG./KG. BODY WEIGHT EVERY 4 HOURS

Patient	Wt. in kg.	Aureomycin dose in mg.	Serum μg./cc. 1st Assay† period 1 hr.	1st Assay† period 4 hr.	2nd Assay period 1 hr.	2nd Assay period 4 hr.	Urine μg./cc.§	Cerebrospinal fluid μg./cc.§	Days of therapy before 2nd assay period
K.W.	9.1	100			1.00	2.00			3
D.N.	11.3	100*				0.44‡		0.20	4
E.D.	10.9	100*			1.16	1.04		0.18	4
N.V.	27.2	250	0.74	0.74	1.40	1.00	320	0.59	4
L.M.	21.3	250				2.40			5
D.G.	10.4	125			0.40	1.14	56		5
R.M.	16.8	150*	1.45	1.75			320		5
J.A.	12.2	150*	<0.20	0.23	0.79	0.75	160	0.50	5
T.P.	20.9	250	4.64	2.76	4.76			0.12	6
T.S.	20.4	250	1.00	1.68	1.84	1.84	131	0.31	6
J.H.	21.8	250			1.46	2.35			6
J.Ma.	22.7	250	2.24	2.16	5.92	1.84			7
C.F.	13.2	125			4.00‡	2.70‡		1.16	8
R.W.	5.0	50	1.80	1.00	0.52	0.54	240	0.46	10
Range			<0.20–4.64	0.23–2.76	0.40–5.92	0.54–2.40	56–320	0.12–1.16	
Mean			1.72	1.47	1.92	1.49	204	0.44	
Median			1.45	1.68	1.46	1.84	200	0.31–0.46	

* Given in chocolate powder dissolved in 2 oz. of milk/50 mg. of aureomycin. The remainder of the patients received aureomycin in capsules or Cartose syrup, followed by 3 to 4 oz. of milk (milk not always taken).

† First serum assay was done 16 to 20 hr. after aureomycin was started.

‡ Not included in average figures. D.N. was vomiting; C.F. had acute glomerulonephritis.

§ Collected at second assay period.

TABLE 4

SERUM LEVELS DURING 6 HOURLY ORAL DOSES OF AUREOMYCIN VARYING FROM 11 TO 17 MG./KG. BODY WEIGHT/DOSE

Patient	Wt. in kg.	Aureomycin* mg.	Serum Concentration in μg./cc. 1 hr.	4 hr.	6 hr.	Day of Rx
C.M.†	9.1	125	4.46	2.74	2.08	2
W.B.	45.8	500	2.14	0.72	1.32	5
M.S.	28.1	500	3.20	4.80	3.52	4
I.C.‡	16.8	250	1.32	1.68	1.36	3
A.W.	39.9	500	1.14	1.56	—	3
M.H.	9.1	100	2.08	1.40	2.08	7

* Given in capsules or removed from capsule and given in Cartose syrup; 3 to 4 oz. of milk offered after each dose.

† Had pyelonephritis. However, retrograde and I.V. pyelograms were normal.

‡ Had chronic pyelonephritis, with atrophic kidney.

Levels obtained 15 minutes after injection range from 3.5 to 16 μg./cc. serum. There is then a fairly rapid fall in serum levels for approximately three hours, so that at the end of that time they range from 1.2 to 4.0 μg./cc. From then on, there is a markedly slower

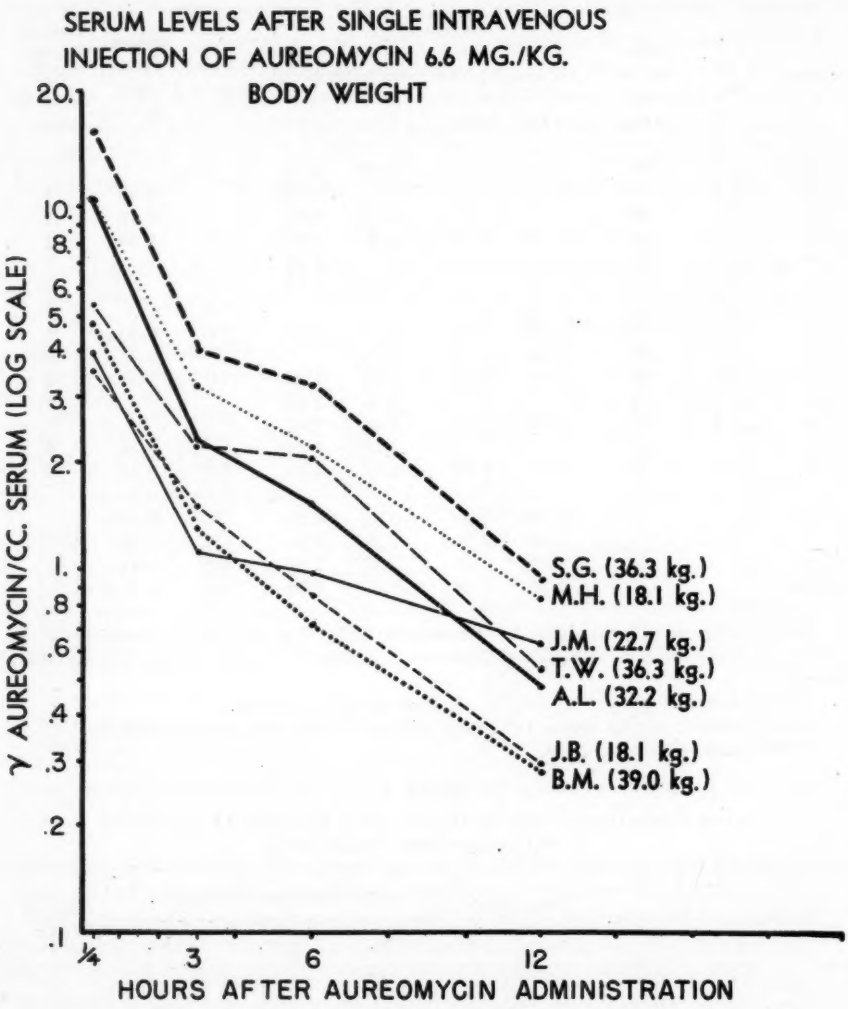


FIG. 1. Aureomycin was injected rapidly in 1-leucine diluent (aureomycin 20 mg./cc.). Weight of patients is in parentheses after their initials.

rate of decrease of serum levels, and the rate of disappearance follows a straight line curve. At the end of 12 hours, levels range from 0.3 to 0.95 μg./cc.

Levels obtained after the intravenous administration of 2.2 mg./kg. body weight are shown in table 6 (first five patients). Levels at ½ hour range from 0.66 to 4.80 μg./cc., and the rate of disappearance of the antibiotic from serum is similar to that seen with the larger dose.

TABLE 5

SERUM LEVELS AFTER SINGLE RECTAL DOSE OF AUREOMYCIN

Patient	Wt. in kg.	Aureomycin* mg.	Aureomycin μg./cc. serum			Aureomycin retained
			1 hr.	3–4 hr.	5–6 hr.	
P.S.	14.5	150†	0.27	—	—	No
D.F.	46.7	500†	0.25	—	—	No
J.J.	24.5	250†	0.31	—	—	No
C.W.	68.0	500†	<0.10	—	—	No
K.J.	34.0	250	<0.10	<0.10	<0.10	Yes
K.J.	34.0	500	<0.10	<0.10	<0.10	Yes
C.W.	68.0	500	0.50	<0.10	<0.10	Yes

* Given in perforated capsules.

† Aureomycin followed with 30 cc. water.

The possibility that carinamide might be effective in prolonging therapeutic serum levels of aureomycin in a similar fashion as in the case of penicillin[10] was investigated. The results are shown in table 6 and in figure 2. No significant effect either in the height of the peak level or in the rate of disappearance of aureomycin from the serum was found.

3. Aureomycin Levels in Other Body Fluids

A. Cerebrospinal Fluid: Spinal fluid aureomycin levels obtained in patients on 11 mg./kg. body weight every four hours are shown in table 3. Detectable levels were found with every determination. The values vary greatly and seem to show no definite correlation with serum levels. There is no data as to the rapidity with which aureomycin diffuses into the

TABLE 6

EFFECT OF CARINAMIDE* IN DOSE OF 0.66 GM./KG. BODY WEIGHT/DAY ON SERUM CONCENTRATION OF AUREOMYCIN AFTER ADMINISTRATION OF SINGLE INTRAVENOUS DOSE OF AUREOMYCIN†

Patient	Wt. in kg.	Mg. of aureomycin	Serum Concentration of Aureomycin in μg./cc.									
			Without carinamide					With carinamide				
			¼ hr.	½ hr.	3 hr.	6 hr.	12 hr.	¼ hr.	½ hr.	3 hr.	6 hr.	12 hr.
M.G.	43.1	100		0.66	0.60	0.27			1.60	0.90	0.39	
S.G.	36.3	80		4.80	2.36	1.30			2.00	0.45	0.45	
A.L.	32.2	75		1.48	0.70	0.55			3.36	0.90	0.82	
J.Ma.	22.7	50		1.52	0.25	0.18			2.06	1.65	0.29	
E.O.	22.2	50		1.64	0.82	<0.20			1.08	0.95	0.36	
A.L.	32.2	225	10.06		2.27	1.54	0.48	5.04		1.82	1.00	0.39
J.Ma.	22.7	150	4.00		1.12	1.00	0.63	3.68		0.91	0.36	0.25

* The carinamide was divided into equal doses and given every 4 hr. orally, beginning 14 hr. before the injection of aureomycin and continued until the last specimen was taken.

† The aureomycin was given in the 1st 5 instances in ⅓ molar sodium lactate in a concentration of 0.5 to 1 mg./cc. and took about 15 min. to run in. Timing of collection of specimens was from time infusion was started. In the last 2 instances, aureomycin was given in the 1-leucine diluent rapidly in a concentration of 20 mg./cc.

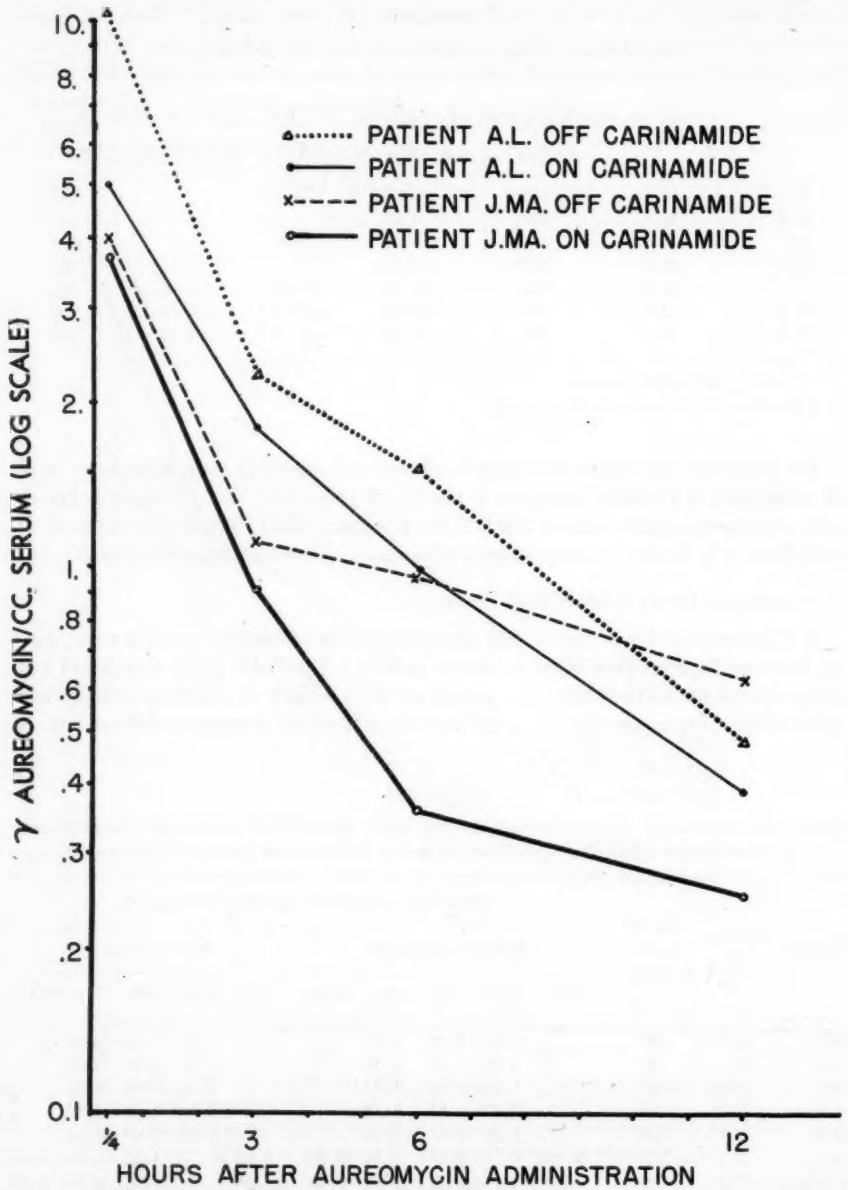


FIG. 2. Comparison of rate of disappearance of aureomycin from serum with and without concomitant carinamide administration (data taken from table 5).

cerebrospinal fluid, since the earliest spinal fluid assay was made after four days of therapy. In none of these patients was there meningeal inflammation.

B. Urine: Urine levels in these patients are also shown in table 3. In figure 3 the

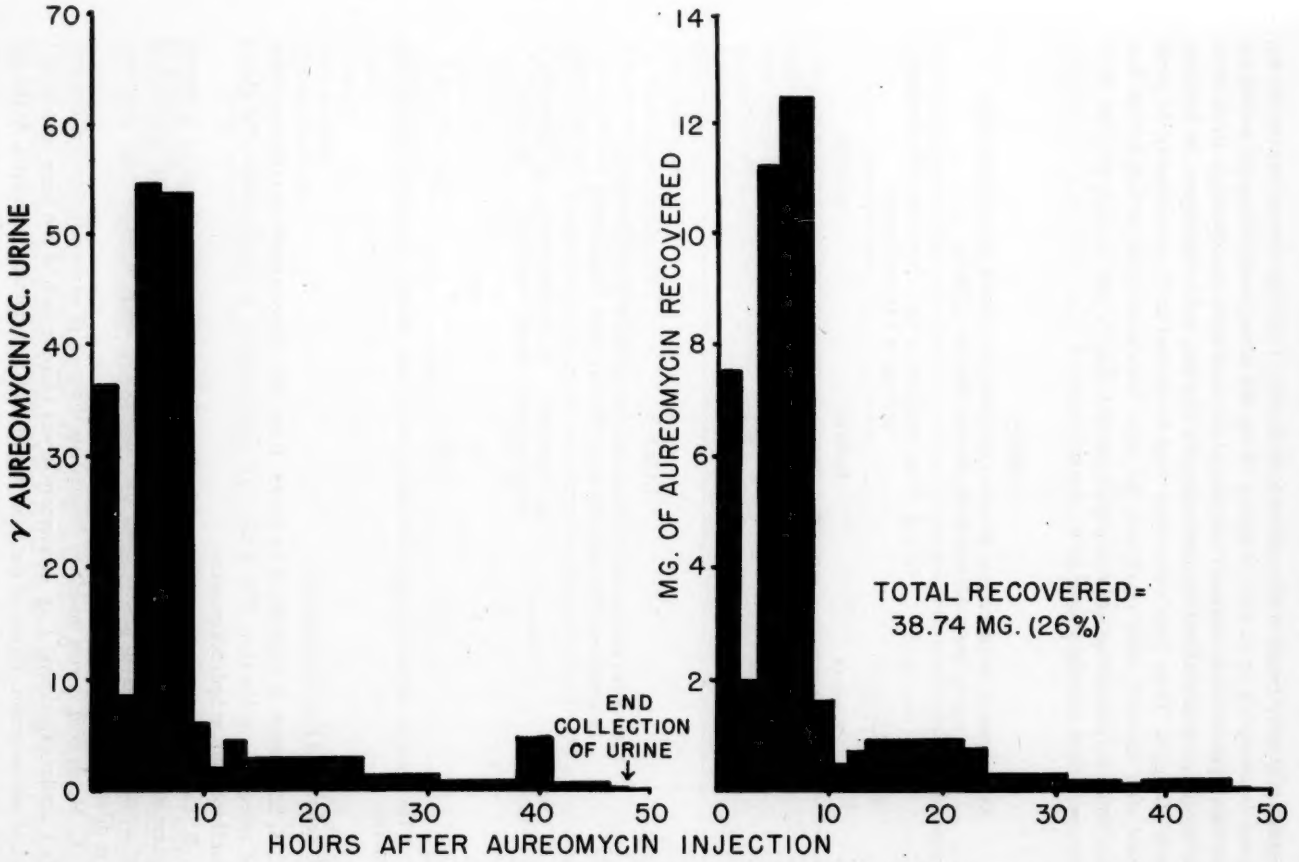


FIG. 3. Recovery of aureomycin in urine after injecting 150 mg. intravenously into 68.0 kg. man.

pattern of urinary excretion of aureomycin is charted. A 150 mg. dose of aureomycin was given intravenously to an adult weighing 68 kg. All urine passed during the subsequent 48 hours was collected, measured and assayed for aureomycin concentration. Urine levels of 38 μg./cc. were obtained two hours after the injection, and in four hours, the level was over 50 μg./cc. These high urine levels were maintained until approximately the ninth hour after injection, after which time the urine concentration fell to 6 μg./cc. or less. Converted to total amounts of aureomycin excreted (Fig. 3, part 2), it is seen that 38.74 mg., or 26% of the total amount given, was recovered.

TABLE 7

COMPARISON OF ANTIBACTERIAL ACTION OF AUREOMYCIN IN SERUM AND IN PHYSIOLOGIC SALINE AGAINST STAPH. AUREUS (OREGON J STRAIN)

Aureomycin μg./cc.	Growth of Test Organism in Klett Units After 4 Hr. Incubation (Average of 3 Determinations)	
	In Serum	In Saline
1.6	11	10
0.8	20	18
0.4	53	48
0.2	76	78

TABLE 8

COMPARISON OF AUREOMYCIN CONCENTRATION IN SERUM WITH OR WITHOUT EXPOSURE TO ERYTHROCYTES FOR ½ HOUR AT ROOM TEMPERATURE

Serum Specimen	Serum cc.	μg Aureomycin Added to Serum	cc. Erythrocytes* Serum Mixed with	μg Aureomycin Recovered
#1	1	1	0.5	1
#2	1	1	0	1

* The serum and erythrocytes were all obtained from the same patient 4 days before the experiment was run.

4. Relevant *in Vitro* Experiments

A. Inactivation of Aureomycin by Serum: It has been demonstrated[6] that the destruction of aureomycin is less than 15% when 1 μg. aureomycin/cc. of human serum is incubated for three hours at body temperature.

B. Table 7 compares the antibacterial effect of aureomycin when dissolved in normal saline solution and when dissolved in human serum. There was no demonstrable binding of aureomycin by serum protein under the conditions of assay, in which serum specimens are diluted 1:10 in assay broth.

C. Meads et al.[11] were unable to demonstrate diffusion of aureomycin into erythrocytes. In a similar experiment, 1 μg. of aureomycin was added to each of two tubes containing 1 cc. of human serum. To one of the tubes was added 0.5 cc. human erythrocytes. At the end of ½ hour at room temperature serum from each tube was assayed. The aureomycin con-

centration in each tube was still 1 μg./cc. (table 8): Thus under these conditions, aureomycin did not appear to diffuse into the red cells.

D. Aureomycin hydrochloride was more soluble in strongly acid and strongly alkaline solutions than relatively neutral solutions in an experiment run by Dr. Seymour S. Cohen.*

5. Clinical Results

A group of patients with various infections, many of them resistant to penicillin and streptomycin, have been treated with oral aureomycin alone in doses of approximately 44

TABLE 9

BACTERIAL INFECTIONS IN CHILDREN TREATED WITH ORAL AUREOMYCIN APPROXIMATELY 60 MG./KG. BODY WEIGHT/DAY DIVIDED INTO 4 TO 6 EQUAL DOSES

Type Infection	No. of Cases Treated	Response			
		None	Improved	Total Remission	Cured
Acute purulent conjunctivitis	1				1
Acute tonsillo pharyngitis	3				3
Acute purulent nasosinusitis	2				2
Acute purulent otitis media	3				3
Acute bronchitis	4				4
Acute pneumonia	3				3
Chronic purulent nasosinusitis	1		1		
Subacute recurrent purulent otitis media*	4			3	1
Chronic purulent otitis media*	4		3	1	
Chronic mastoiditis	1			1	
Chronic bronchitis	2		1	1	
Chronic skin infections†					
Sycosis barbae	5 (adults)		1	4	
Leg ulcer	2		1	1——→?	
Furunculosis	1			1	
Infected eczema	2 (adults)		2		
Single furuncle	1				1
Urinary tract infections					
Acute	1			1——→?	
Chronic	6		2	4	
Acute pertussis	3	2			1 ? by drug
Chronic osteomyelitis	1		1——→?		

* Studied with Dr. Nicholas Hoffman, Otolaryngology Department.

† Studied with Dr. Harvey Blank, Dermatology Department.

to 66 mg./kg. body weight/day. These are presented in tabular form in table 9. Careful bacteriologic studies were not uniformly performed on these patients, but predominating organisms were: staphylococci, streptococci, and pneumococci in the acute respiratory infections, gram negative rods in the chronic urinary tract infections, staphylococci in the chronic dermatitides, and staphylococci and gram negative rods in the chronic middle ear infections. The most striking clinical finding so far has been the response of indolent

* Research Biochemist.

localized infections such as chronic pyodermia and chronic otitis media to orally administered aureomycin.

Discussion

Dosage: From these studies it appears that aureomycin in doses of approximately 11 mg./kg. body weight given orally at four hour intervals is well tolerated by the great majority of infants and children. Although highly variable, the serum levels resulting from such a dosage schedule are generally at or above the effective *in vitro* inhibitory concentration for most sensitive organisms (table 10).* In addition, most of the bacterial, viral,

TABLE 10

In Vitro Sensitivity of Bacteria to Aureomycin* [1,9,12–15]

I. Bacteria Highly Sensitive to Aureomycin (usually sensitive to $<1\mu$g./cc.):	
Str. pyogenes	B. anthracis
Staph. pyogenes	C. diphtheriae
Pneumococcus	C. xerose
N. gonorrhoeae	Cl. histolyticum
N. meningitidis	Cl. parabotulinum
H. hemolyticus	Cl. perfringens
H. influenzae	Cl. septicum
H. pertussis	Cl. sporogenes
Pleuropneumonia-like organism	Cl. tetani
B. subtilis	V. comma
Br. suis	
Br. abortus	
Br. bronchiseptica	
II. Bacteria Moderately Sensitive to Aureomycin (usually sensitive to 1 to 10 μg./cc.):	
Str. faecalis	S. choleraesuis
Esch. coli	S. paradysenteriae
S. typhosa	S. gallinarum
III. Bacteria Relatively Resistant to Aureomycin (usually resistant to $<10\ \mu$g./cc.):	
A. aerogenes	P. aeruginosa
Pr. vulgaris	K. pneumoniae

* Read after 18 hr. or more of incubation.

rickettsial, spirochetal and protozoan infections which have been reported as being treated successfully with aureomycin have been on oral dosage schedules roughly comparable to the one used here with or without small intramuscular supplementary doses.[1,9,16–29] Single doses larger than 11 mg./kg. body weight do not appear to produce significantly higher serum levels. For this reason a large initial booster dose has not been used. Smaller individual doses or more infrequent doses may prove satisfactory in many cases. The same total

* It is well to remember that *in vitro* aureomycin sensitivity tests as currently run do not actually measure the effective minimum inhibitory (*i.e.*, bacteriostatic) concentration of aureomycin, since aureomycin is destroyed in appreciable amounts during the 18 to 24 hours before the test is read (as shown by Chandler and co-workers[1]). However, the aim in oral therapy is to achieve concentrations of aureomycin in the optimal bactericidal range for sensitive bacteria. Preliminary *in vitro* studies by Paine and co-workers[12] suggest that the serum levels previously referred to are probably necessary to approach the optimal bactericidal range for sensitive bacteria.

The possibility that concomitantly administered milk might reduce the amount of oral aureomycin absorbed must also be considered in interpreting the data presented here.

daily dose (60 mg./kg. body weight) divided into less frequent individual doses than every four hours might or might not prove equally effective and well tolerated. One cannot tell from this data.

In patients unable to take aureomycin by mouth, and in infections requiring intensive treatment and high serum levels, the intravenous route seems to be the most desirable method for parenteral administration. The tentative dosage schedule of 6.6 mg./kg. body weight intravenously every 12 hours seems reasonable. A single intravenous dose of aureomycin 6.6 mg./kg. body weight followed by oral aureomycin thereafter may be desirable at times.

Frequent febrile reactions, local pain and inflammation, and poor serum levels have dissuaded the authors from using the intramuscular route.

Judging from the limited data, rectal administration seems too unreliable for routine use, whether water is added to enhance the absorption or not.

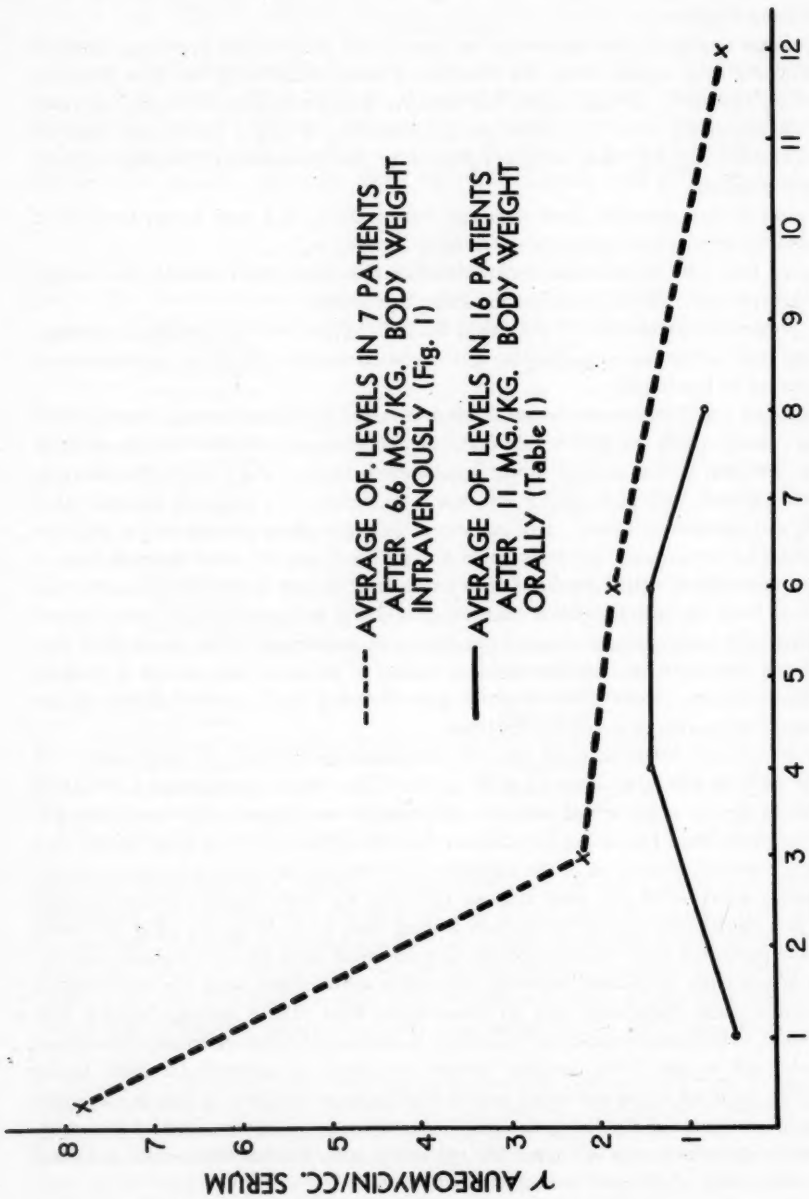
The presence of aureomycin in the spinal fluid of children with noninflamed meninges receiving oral aureomycin suggests that intrathecal aureomycin would be unnecessary in the treatment of meningitis.

Absorption and Distribution: Serum levels determined at regular intervals over a period of 6 to 8 hours (table 1) after single oral doses of aureomycin follow a fairly uniform pattern. The peak level is attained slowly, somewhere between 1 and 4 hours after the drug has been ingested. This peak level is low, but is maintained at a relatively constant value until 6, and sometimes 8 hours after ingestion. This is in sharp contrast to the situation obtaining after intravenous injection (table 6 and Figs. 1 and 4). Here the peak level is obtained immediately with a prompt fall in serum level. It may therefore be inferred that absorption from the gastrointestinal tract proceeds slowly and regularly for several hours. The absence of progressing or marked cumulation of aureomycin in the serum after prolonged oral administration together with the failure of increased oral dosage to produce significantly higher serum levels suggests some limiting factor in the ability of the gastrointestinal mucosa to absorb the antibiotic.

The peak serum levels obtained after the intramuscular injection of streptomycin 6.6 mg./kg. body weight range from 12 to 27 μg./cc.[30] This range approximates a calculated value of 33 μg./cc. which would obtain if streptomycin were equally distributed throughout extracellular fluid (assuming extracellular fluid to represent 20% of body weight, and assuming complete absorption of the antibiotic). In the case of aureomycin, however, the intravenous injection of the same amount (6.6 mg./kg. body weight) results in peak values of a much lower order of magnitude ranging from 3.5 to 15 μg./cc. (Fig. 1). Study of already published data[10] also reveals that the peak serum level after intravenous administration of penicillin to children receiving carinamide approximates what one would expect if penicillin were distributed only to extracellular fluid. These findings suggest that aureomycin, unlike streptomycin and penicillin, is distributed rather uniformly throughout the body, rather than being confined almost exclusively to extracellular fluid. Rapid destruction, rapid excretion and serum protein binding seem ruled out by this data as possible significant causes of the low peak serum aureomycin levels obtained here.* However, aureomycin apparently does not enter the red blood cells. Further work seems indicated on the distribution of this antibiotic in the body.

Without more knowledge of the body distribution of aureomycin, no final conclusions

* Binding of aureomycin by the serum protein is not ruled out by this experiment, but if any binding occurs, it is apparently reversed by the dilution of serum during assay.


γ AUREOMYCIN/CC. SERUM
8
7
6
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1 2 3 4 5 6 7 8 9 10 11 12
HOURS AFTER AUREOMYCIN ADMINISTRATION
----- AVERAGE OF LEVELS IN 7 PATIENTS AFTER 6.6 MG./KG. BODY WEIGHT INTRAVENOUSLY (Fig. 1)
— AVERAGE OF LEVELS IN 16 PATIENTS AFTER 11 MG./KG. BODY WEIGHT ORALLY (Table 1)

FIG. 4. Comparison of serum aureomycin levels after intravenous and oral administration.

from the data on the mechanism of renal excretion are possible since determination of the mode of renal excretion from the slopes of serum level curves requires a knowledge of body distribution of the drug in question. However, the slow rate of disappearance of aureomycin from the serum plus the fact that carinamide in doses known to block the tubular excretion of penicillin[10] does not seem to affect the slopes of the aureomycin serum level curves suggests that tubular excretion plays a negligible role and that renal excretion is glomerular alone.

Photosensitivity: The question of photosensitivity being induced by aureomycin ingestion is being studied further. Until a final answer is obtained avoidance of exposure to the sun during aureomycin ingestion is suggested.

Summary

Data are presented on the administration, absorption, distribution and excretion of aureomycin in children. From these data, tentative oral and intravenous dosage schedules of, respectively, 11 mg./kg. body weight every 4 hours and 6.6 mg./kg. body weight every 12 hours are proposed. The same total daily oral dose (60 mg./kg. body weight) divided into less frequent individual doses than every four hours might prove equally effective and well tolerated. The possibility of uptake of aureomycin by some or all the cells of the human body is also suggested. The observation of apparent photosensitivity occurring during aureomycin ingestion is reported.

Addendum

Since this manuscript was submitted for publication, Batholomew and Nichols have shown (Proc. Staff Meet., Mayo Clin., June 21, 1950) that concomitantly administered milk does not influence the absorption of orally administered aureomycin to human adults as does aluminum hydroxide gel. These workers were able to reduce the incidence and severity of gastrointestinal symptoms from orally administered aureomycin with concomitantly administered milk, corroborating the present authors' statement to this effect. The study of these two workers makes the data presented in the preceding manuscript easier to interpret and compare to other similar data on adults and children, since most, but not all, of the children receiving oral aureomycin in the present study also received milk with each dose (see footnotes in tables).

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SPANISH ABSTRACT

Estudio sobre la Administración, Absorción, Distribución y Excreción de la Aureomicina en Niños con Observaciones Concernientes a la Tolerancia, Dosificacion y Ciertas Indicaciones Terapeuticas

Se presentan data sobre la administración, absorción, distribución y excreción de la aureomicina en niños. Los autores sugieren la siguiente dosis y forma de tratamiento: 11 miligramos/kilogramos de peso cada cuatro horas y 6.6 miligramos/kilogramos de peso cada doce horas. La misma dosis total diaria (60 miligramos/kilogramos de peso) puede ser dividida en tomas individuales menos frequentes con una tolerancia y eficacia posiblemente similar. La posibilidad que la aureomicina es absorbida por algunas o todas la celulas del cuerpo humano es sugerida. Se reporta la observacion de una "photosensitivity" aparente durante la ingestion de la aureomicina.

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TREATMENT OF MIXED TUMORS OF THE KIDNEY IN CHILDHOOD

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CONTRARY to the conditions which existed a decade ago, pediatricians and practitioners are now increasingly aware of the existence of malignant disease in infancy and childhood. This changing attitude is partially responsible for the improved results of therapy, since success so often depends upon the promptness with which neoplasms are detected and treated. While many forms of malignancy still carry a hopeless prognosis, it has become quite clear that a reasonably high proportion of children with embryomas of the kidney can be cured.

Though not the first to describe these renal tumors, Wilms[1] did much to focus attention on them by his classical paper on the subject. "Wilms' tumor of the kidney" is a term which is widely used to indicate a mixed type of growth which is found in infancy and early childhood, is seldom seen beyond the age of 10 or 12 and is very rare in adult life. It should not be confused with the hypernephroma, or Grawitz tumor, which is most common in later life and is almost unknown in childhood. An embryoma can contain any type of structure which develops from mesoderm. The cellular components may be anaplastic and undifferentiated, but there are tendencies in some areas for cells of an epithelial type to form acinar spaces or abortive renal tubules. Connective tissue, angiomatous structures, smooth muscle, striated muscle and occasionally bone or cartilage may be found in varying amounts. Representative blocks from a tumor show many of these elements in different combinations. The multiplicity of microscopic pictures has given rise to many descriptive terms, depending upon the predominating features. Thus the growths have been reported as "renal carcinoma," "sarcoma," "angiosarcoma," "rhabdomyosarcoma," etc. The present authors prefer to avoid such designations and group all these tumors under the general name of embryoma, or mixed tumor of the kidney. For the past two decades in this hospital, all pathologic material has been carefully studied by Dr. Sidney Farber, who has long been particularly interested in the neoplasms of early life and has contributed so much to knowledge concerning them.

These lesions (Fig. 1) may be the size of a fist, are commonly as large as a grapefruit, and sometimes are bigger than a football. Since the growth presumably arises from an embryonic rest within renal substance, the enlarging mass continues to expand around itself the capsule of the kidney; this layer may be enormously distended but it tends to remain intact for a long time and thus serves to prevent the neoplasm from invading adjacent organs (Fig. 2). The growths are spherical or oblong; they have a smooth or only slightly lobulated surface. Cystic or hemorrhagic degeneration is frequently found. The neoplasm tends to be sharply demarcated from the kidney substance which is com-

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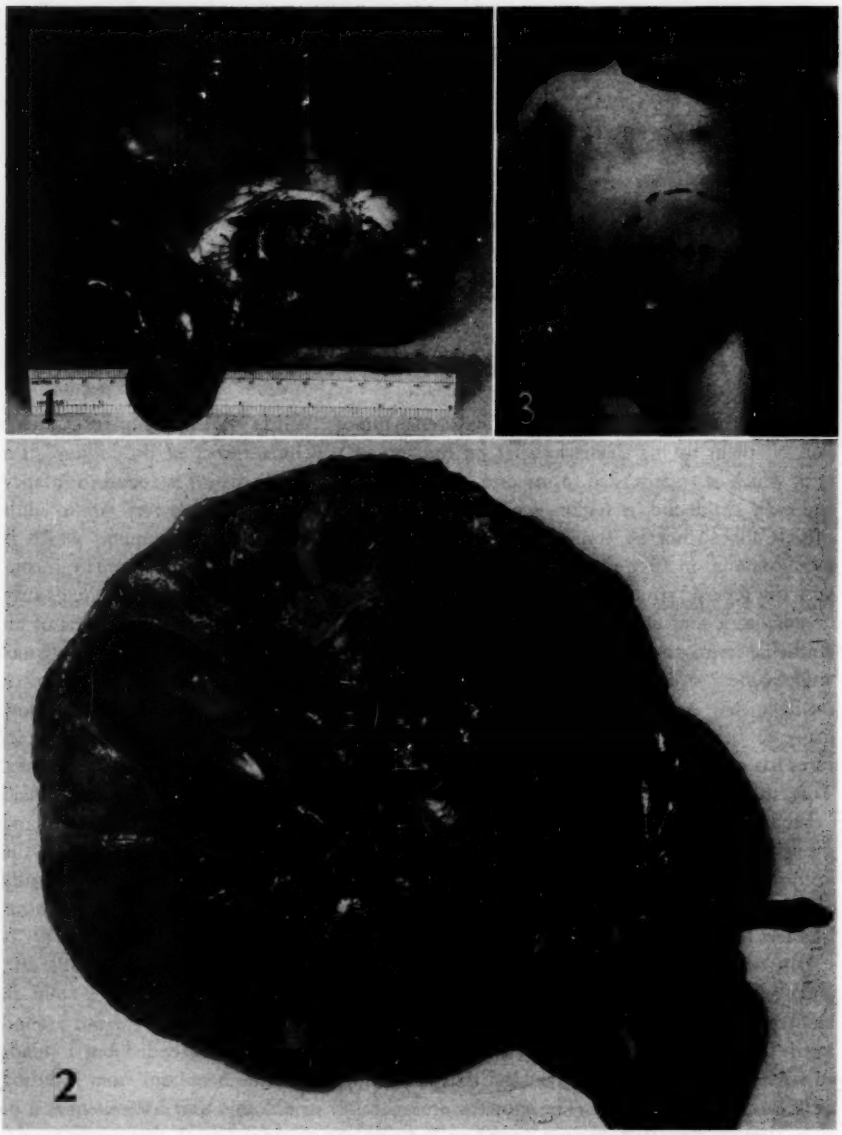

FIG. 1. Large embryoma of kidney, excised from 6 yr. old child.

FIG. 2. Cut surface of mixed tumor of kidney. Neoplasm developing within renal tissue, distends around itself kidney capsule. Areas of necrosis and liquefaction appear in neoplasm. Renal pelvis is compressed and distorted, but is not invaded.

FIG. 3. Child with embryoma of left kidney. Skin markings show outline of mass.

pressed and distorted. The renal pelvis is seldom invaded, but it is usually narrowed, elongated or otherwise deformed.

The primary complaints seldom include more than a sudden awareness—on the part of parent or physician—that a large, hard mass is palpable, or that the abdomen appears distended. It is amazing to find that such a sizable and silent structure can appear without having given some previous warning of its presence. Pain and discomfort are uncommon. Occasionally there is pallor if the nutrition has been interfered with, but this is the exception rather than the rule. Urinary complaints are rare. Hematuria is seldom encountered, but its appearance is an extremely unfavorable sign. The authors' youngest patient was 3 weeks of age; the vast majority of subjects were under 4 years.

By physical examination, a hard mass is found in either upper quadrant and extends well back into the renal fossa, a point which will help to rule out hepatomegaly on the right and splenomegaly on the left. Small growths can be moved somewhat, but larger ones are apt to be fixed. The smooth contour and the limitation to one side of the body (Fig. 3) help somewhat to differentiate embryomas from neuroblastomas which are prone to have a pebbly surface and a greater tendency to spread across the midline. Mild or moderate hypertension is found in some cases. Embryomas appear with about equal frequency on the two sides; in four of these cases they were bilateral and apparently represented primary growths in each kidney. Some fever is usually present when there is tissue necrosis in the tumor. It would seem unnecessary to differentiate an embryoma from a painless hydronephrosis, yet it is sometimes impossible to do this by physical examination alone.

Roentgen examination should include an intravenous pyelogram, performed for the purpose of determining the presence and condition of the opposite kidney and also for gaining valuable information regarding the mass and its relation to the ipsilateral kidney. With an embryoma, it is very rare to have no excretion of dye on the affected side; the renal pelvis can usually be visualized either within the shadow of the mass or pushed to the periphery thereof. The kidney pelvis is apt to be greatly distorted and also displaced (Fig. 4) forward or backward, upward or downward, medially but seldom laterally. Intravenous pyelography usually gives all the information which is required, but if this is not satisfactory, retrograde pyelograms should be made (Fig. 5). In the presence of an abdominal neoplasm, complete study and evaluation of a case necessitates a search for metastatic lesions. Embryomas metastasize primarily to the lungs; neuroblastomas have a much greater predilection for invasion of the skeleton, with involvement of lungs only late in the course of the disease.

Treatment

As a first step in treatment of this very malignant tumor in infancy and childhood it is necessary to dispel the feeling of gloom and hopelessness which has long been expressed by many who have handled these cases. It is still true that even modern therapy is frequently followed by disappointment and failure, but there is a brighter side of the picture when we see an increasing percentage of cures following early and thorough attack on the problem.

When summing up the results in a series of cases from any one hospital, authors should feel obliged to include all cases they have encountered in which the diagnosis of embryoma was proved or was reasonably well established; only against such a background can the cures be presented to calculate the true percentage of survivors. There has

been a widespread tendency to report series of the more hopeful cases (patients who have been operated upon or otherwise treated) and to use this number when calculating the percentage of cures which result therefrom. The figure thus obtained indicates the results in the treated cases, but it certainly does not tell what is happening to the entire group of patients encountered in a given institution. Such considerations should be taken into account when scrutinizing published reports.

Malignant tumors of the kidney in childhood can be treated by roentgen irradiation alone, by excision (with or without irradiation) and by chemotherapeutic agents. Of the latter, nothing will be mentioned here since there is little of value which can be offered at this time; however, the rapid strides which are being made in this field for the

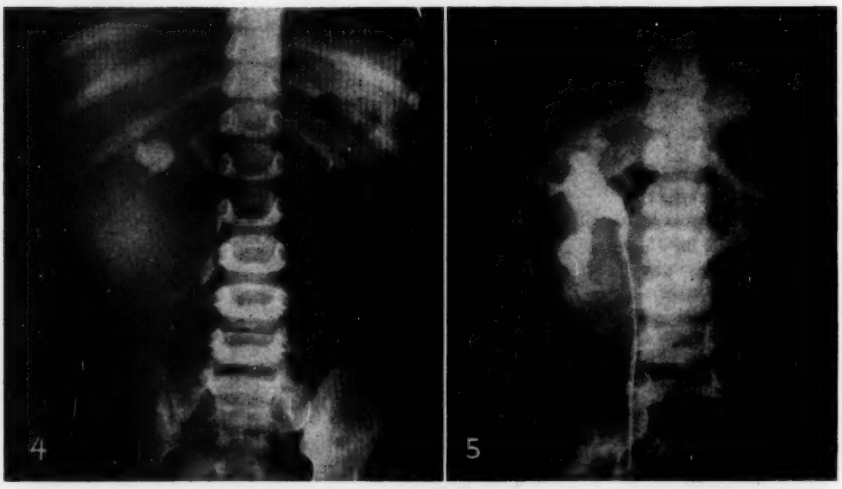

FIG. 4. Intravenous pyelogram from child with embryoma of right kidney. Note shadow of mass which expands right flank. Left kidney present and normal. Right renal pelvis (arrows) is greatly distorted and pushed toward midline.

FIG. 5. Retrograde pyelogram which was made because intravenous pyelograms were unsatisfactory. On patient's right is large mass, lying anterior to pelvis and calyces, with flattening and distortion of pelvis.

treatment of some other forms of neoplasm raise the hope that chemical agents or radioactive compounds will be found to control Wilms' tumors which have already metastasized to various parts of the body. The literature contains many reports on the treatment of renal embryomas by surgery, irradiation, or by combinations of the two. No attempt is made herewith to mention all these articles; only the more impressive ones will be summarized.

Weisel, Dockerty and Priestley[2] in 1943 reported 7 cures in 44 patients, in 42 of whom the treatment included nephrectomy—a cure-rate of 16%. For some of their patients irradiation was employed postoperatively, in others such treatment was given both before and after operation. While their material gives convincing evidence of the power of roentgen rays to shrink many of these neoplasms and thus make easier their operative removal, the data are not presented in any way which proves that radiation increases the number of cures over that which can be obtained by surgery alone.

Dean[3] in 1945 summarized his findings in the treatment of 20 patients by irradiation only, of whom five were still alive without evidence of disease for more than five years. In none of these was a positive diagnosis established by biopsy; this raises the slight possibility that some of these youngsters may actually have had other types of neoplasm. Dean does not recommend therapy by irradiation alone, admitting that combinations of roentgen treatments and nephrectomy would probably give superior results. While his series is open to some criticism regarding diagnostic accuracy, the material does give considerable evidence regarding the destructive effects of roentgen rays on some of these growths.

TABLE 1

THERAPEUTIC STATISTICS FROM SILVER'S SERIES

Treatment	Outcome	
	Alive	Dead
No therapy	0	2
Irradiation alone	0	3
Nephrectomy alone	3	1
Nephrectomy plus postoperative irradiation	3	2
Preoperative irradiation, nephrectomy and postoperative irradiation	4	0

Nesbit and Adams[4] in 1946 presented a series of 16 children with Wilms' tumors; 12 of these had nephrectomies (a few with postoperative radiation) with seven cures, a survival rate of 58.4%. Another was treated by biopsy and irradiation, with cure. The survival of 8 out of 16 patients in whom the diagnosis of embryoma was positively made, gives a combined cure-rate of 50%. In the same 10 year period they observed 11 other patients in whom a presumptive diagnosis of embryoma was made but for various reasons was never confirmed by pathologic examination. It is possible that some of these children did not have embryomas, but the evidence recorded by these experienced men would suggest that most of these subjects actually did have embryomas; 7 (possibly 9) are known to have died subsequently. Thus if one considers the entire group of 27 patients with proved or probable embryomas of the kidney, the over-all cure percentage would be somewhere in the middle or upper thirties.

Silver,[5] in a series of 18 cases reported in 1947, had 10 survivals, a figure of 55%. A closer inspection of his material shows inclusion of 2 adults (21 and 27 years), so that if one is considering only the problem in childhood ages, there were 16 cases and 8 survivals, a cure of 50%. No standard treatment was employed. While the small number of cases with each type of therapy might possibly lead to erroneous conclusions, the valuable data reported by Silver are certainly worthy of study and are summarized in table 1. The last group, while small, is particularly noteworthy.

Dickey and Chandler[6] in 1949 reported 12 cases of Wilms' tumor in which the diagnosis was confirmed by examination of the gross or microscopic tissue; 4 patients survived (33%). The treatment had been transperitoneal nephrectomy, followed (in some instances) by postoperative irradiation.

A brief review of the present investigators' material from the Children's Hospital of

Boston provides the basis for some comments and conclusions. All patients seen in the hospital who have had an embryoma of the kidney have been counted whether treated or not; therefore the series includes some who had metastatic disease when first seen, and for whom only palliative treatment and terminal care could be offered. Patients treated up through 1947 have been studied because it is now two years since their treatment and it is possible to make reasonably accurate statements regarding the cures and the failures. The 96 children have been under the care of various members of the staff; the first 60 of these were analyzed by Ladd and White[7] in 1941. The data are summarized in table 2, the material being divided into three groups, 1914-1930, 1931-1939 and 1940-1947, because the methods of treatment varied greatly in these three periods.

TABLE 2

STATISTICS FROM BOSTON CHILDREN'S HOSPITAL SERIES OF MIXED TUMORS OF KIDNEY

Period of Study	Probable Cures		
	Patients below 12 mo. of age	Patients above 12 mo. of age	All patients of all ages
1914–1930 Inclusive 27 Cases (4 Cures)	42.8%	5.0%	14.9%
1931–1939 Inclusive 31 Cases (10 Cures)	71.4%	20.8%	32.2%
1940–1947 Inclusive 38 Cases (18 Cures)	80.0%	43.3%	47.3%

From 1914 through 1930 there were 27 cases, with 4 cures, a survival of 14.9%. During this time no special attention was paid to this neoplasm; patients were operated upon by a number of visiting surgeons. The operative mortality alone was 23%. It is not surprising to find that the haphazard methods then employed were followed by so few long-term survivors.

From 1931 through 1939 there were 31 patients and a sharp rise in the cures to 32.2%. This great improvement can be attributed entirely to the efforts of Dr. William Ladd who became interested in the problem and promptly introduced changes in the technical aspects of the surgery to eliminate the hazards previously associated with such surgical undertakings. Proper anesthesia was acquired, intravenous fluids and blood were given to prevent shock, a transabdominal approach was universally employed to facilitate removal of the larger growths and to allow early division of the renal vessels. Attention to technical details quickly led to elimination of deaths on the table and in the immediate postoperative period; after 1932 there were no deaths from operation in spite of the fact that all tumors were removed, regardless of their size. Many of these neoplasms were enormous; in one instance the weight of the growth was one-quarter that of the child. Improving the operative technic was richly rewarded by cure-rates which were higher than any that appeared in the medical literature of that time.

From 1940 through 1947, there have been 38 patients and 18 apparent cures, a

survival of 47.3%. Essentially, the surgical procedures have been the same as those developed in the 1931-1939 period; there have been no operative fatalities. Preoperative irradiation has not been employed, and tumors have been excised irrespective of the great size of many of them. It is quite possible that neoplasms were being sent earlier for operation because of the increasing interest of pediatricians and practitioners in this area; this factor is very difficult to evaluate, but we must recognize that prompt detection certainly contributes to a higher probability of cure. However, all the cases could not be regarded as particularly favorable ones, since some of the tumors greatly distended the abdomen. This 1940-1947 group differs from the one of 1931-1939 primarily by the fact that postoperative roentgen irradiation was given in all (except two) cases. The rise in cures to 47% is attributed largely to this routine use of roentgen ray treatments over the renal fossa. It has been the authors' custom to begin these immediately after completion of the operation, before the patient recovers from anesthesia. They are given in daily doses of 200 r, alternately using three portals, anteriorly, laterally and posteriorly over the tumor bed, reaching a total of 4,000 to 5,000 r (measured in air), employing a 200 KV machine, filters of 1 mm. of aluminum and 0.5 mm. of copper, with a target-skin distance of 50 cm., H.V.L. = 1.05 mm. cu. In no case have the authors had difficulties in healing of the abdominal wound.

Eleven of the patients (in the 1940-1947 group) were given some irradiation over the chest (from 400 to 2,000 r, most of them from 800 to 1,200 r). In three instances this was done because of obvious pulmonary metastases, in one because of a widened mediastinal shadow which might have represented tumor, and in seven because examination of the nephrectomy specimen showed tumor in veins and it was thought desirable to attempt killing off any cells which might already have seeded to the lungs. The authors are skeptical about what has been gained by these treatments over the thorax. Certainly no one has been cured who had unquestionable pulmonary metastases (though the lives of three patients were apparently prolonged thereby). It is doubtful if anything can be accomplished by "prophylactic" irradiation, since light doses are probably ineffectual in killing implanted tumor cells, and heavy doses to both lungs sufficient to kill cells will be lethal to the subject.

What can be said regarding the value of roentgen radiation over an embryoma of the kidney prior to its operative removal? Roentgenologists and surgeons have long agreed that such preliminary treatment will generally shrink the mass and make easier its operative removal. Some have felt that it likewise reduces the mortality of operations, but the present investigators agree with Ladd and White that it is possible to remove all these growths safely without preliminary shrinkage. A decision for or against preoperative irradiation should be concerned mainly with its efficacy in increasing the number of cured children. Unfortunately, no convincing proof is available in the literature on this point. Most authors who have advocated preoperative treatments have no statistical data to support their assertions, and indeed the vast majority of them have presented survival figures which are not as good as those which have been published from this hospital wherein roentgen ray treatment was purposefully withheld until after operation. Ladd has always been a strong opponent to preoperative irradiation, believing on theoretic grounds that (1) any delay which put off operation would increase the chances of metastasis and (2) liquefaction of the tumor mass by roentgen rays would enhance the probabilities of malignant cells breaking out into the blood-stream. It is well, however, to reflect upon the four patients treated by Silver with radiation both before and after

nephrectomy—all of whom survived. This group is much too small to permit any sweeping conclusions, though it is a lead which should encourage further study of the subject. At the present time the authors are treating a number of children with preoperative irradiation, hoping to obtain a series large enough to give some irrefutable statistics on the harm or the value of this adjunct.*

The presence of embryomas in both kidneys (in the absence of metastases to the chest) does not necessarily present an insuperable problem. Of the four such cases which have come to the authors' attention, three have died of widespread metastases, but one is apparently cured. This surviving patient was first seen in 1940 at which time there was a very large mass in each kidney area, the right one being somewhat bigger than the left. At transabdominal exploration each renal fossa was found to be filled with a massive tumor which had all the gross characteristics of a renal embryoma. A biopsy of the right one showed microscopic evidence of such a mixed tumor. Following this exploration, roentgen irradiation was given to the abdomen (2,650 r) which had a remarkable effect in reducing the size of the masses—only to be followed some months later by return to their original size. Seven months after the first exploration, a second operation was undertaken by Dr. Ladd, at which time a right nephrectomy was performed and the left kidney was palpated and inspected through the open abdomen. On the left was a mass, somewhat irregular in shape, but having a volume larger than a grapefruit. It had all the external gross characteristics of an embryoma of the left kidney; unfortunately no biopsy of it was taken. Following operation irradiation was given; 750 r over the right renal fossa, 1,350 r over the left sided mass, and 600 r over the lung fields. Subsequent palpations showed that the left renal mass gradually shrank. In their paper of 1941, Ladd and White reported this patient as alive but "hopeless"; the present authors are happy now to give a subsequent note on the case and say that nine years later the child is alive and presents no evidence of neoplastic disease.

What can be said regarding curative effects of irradiation on regional extensions or upon pulmonary metastases? Nesbit and Adams list two instances wherein removal of a renal embryoma was known to be incomplete because regional, retroperitoneal infiltrations were left behind; these were successfully treated by roentgen irradiation. They mention a third case (proved by aspiration biopsy of a right-sided primary tumor and with questionable roentgenologic evidence of right-sided chest metastases) who was treated solely by irradiation over the right side of the thorax and abdomen and who was alive and well 10 years later. Kerr[8] treated a four year old girl by nephrectomy; there was subsequent development of pulmonary metastases which cleared after irradiation. The youngster was alive, well, and without demonstrable disease 52 months later. Silver treated a 21 month old child by nephrectomy and postoperative abdominal irradiation; pulmonary lesions developed seven months later, and the chest was given an unspecified amount of irradiation. The patient was alive and well more than two years later without evidence of recurrence. The present investigators' material presents no

* Since submitting this paper for publication, the authors have studied a series of patients by giving them preoperative radiation (2000-3000 r) before nephrectomy and postoperative radiation. Four children have been treated by this combination; all four have subsequently died with metastases. The authors are therefore abandoning preoperative radiation, firmly convinced that the best over-all results in any extended series will come from immediate surgery, followed quickly by postoperative radiation over the renal fossa.

definite evidence to show that irradiation to chest metastases was of more than temporary benefit. There have been, however, several children, treated by nephrectomy, but in whom extensions of neoplasm were known to be left around the aorta or vena cava; the long-term survival of these must be attributed to the postoperative irradiation which was given. To sum up these impressions—based on rather scanty evidence from their own material and from the literature—the authors feel that three general statements can be made regarding roentgen treatment of neoplastic extensions or metastases. First, if no metastases can be found outside of the abdomen, but if extensions (or metastases) of tumor are found in the abdomen at the time of nephrectomy or subsequent thereto, such abdominal growths should receive extensive and repeated series of treatment because there is a fighting chance that these can be brought under control and can even be eradicated. Second, if there are widespread metastases to the lungs, roentgen therapy (while it may prolong life slightly) has little merit and is hardly worth giving. Third, if there are only a few isolated metastases in the lungs, it is probably desirable to treat these intensively and repeatedly, as long as there is no evidence of important spread to other parts of the lungs.

It is important to add a note regarding prognosis in relation to the age of patients when first treated. A study of these cases has consistently shown that babies in the first 12 months of life have a far better outlook than do older subjects. This is particularly emphasized in the last group (1940-1947) wherein the cures in patients of all ages have been 47%, while in the portion below 12 months of age the cures have been 80%. The reason for this striking difference is unknown. Repeated review of pathologic material does not show any essential difference in the histologic make-up of tumors in the younger and older groups. It is quite possible that the better outlook for babies is related to the fact that infants are examined more often by physicians and that they are handled more frequently by the mother who bathes, changes, and otherwise cares for them; it is quite probable that these lead to earlier detection of intra-abdominal masses.

Parents are always anxious to know how long it will be before they can feel that their treated child is free from the danger of recurrence. A review of the authors' treated cases shows that if recurrence was to take place, it was always evident (by palpation of a mass within the abdomen or by discovery of metastases in a chest roentgenogram) within nine months, except in two instances when it was first manifest at 20 months and at five years. The vast majority of deaths from recurrent disease occurred within one year. These observations indicate that if a patient survives operation for a year and a half without evidence of recurrence, it is probable that a permanent cure has been attained.

Summary

Mixed tumors of the kidney in infancy and childhood can be easily recognized in most instances by simple procedures of physical examination and pyelography. In general, it is not difficult to differentiate them from other masses which can appear in the upper quadrants of the abdomen. Therapy in all instances should include transabdominal nephrectomy and postoperative roentgen irradiation to the area. Whether preoperation irradiation has any advantage other than reducing the size of the mass and facilitating its operative removal is still unproved in the authors' experience or in any literature which has appeared to date. By immediate nephrectomy, combined with routine postoperative irradiation to the operative site, survivals (from 1940 through 1947) have been 47% in children of all ages; in babies under 12 months of age the survivals have been 80%.

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SPANISH ABSTRACT

Tratamiento de los Tumores Renales Mixtos en Niños

Los tumores renales mixtos en la infancia y niñez pueden ser facilmente diagnosticados en la mayoria de los casos con procederes simples, tales como el exámen fisico y la pielografia. En general no es dificil diferenciar estos tumores con otras masas localizadas en el quadrante superior abdominal. La terapeutica en todos estos casos debe incluir la nefrectomia transabdominal seguida con la irradiacion postoperatoria del area. En cuanto al valor de la irradiacion preoperatoria, a excepción de la reduccion del tamaño del tumor, lo que facilita su extirpacion, no tiene otras ventajas probadas de acuerdo con la experiencia de los autores y de otros reportes recientes. Con la nefrectomia immediata combinada con la irradiacion post-operativa del area, el promedio de curas de los autores (1940-1947) ha sido de 47% en niños de todas las edades; y de 80% de curas en niños menores de 12 meses de edad. Ultimamente y en un esfuerzo de mejorar los promedios de curas, un estudio se está realizando en una serie de pacientes a los cuales la irradiacion pre-operatoria ha sido añadida en el tratamiento. Por el momento no puede hacerse comentarios definitivos en favor o contra de la irradiacion pre-operatoria.

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STUDY OF ADOLESCENT CHILDREN INOCULATED WITH BCG IN EARLY INFANCY

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ALTHOUGH BCG has been used as a prophylactic agent in the prevention of tuberculosis since 1921 and although it is still being widely used throughout the world, its usefulness remains controversial. Numerous questions require answers prior to acceptance of this vaccine as a public health measure. Among these questions are included the degree and duration of immunity conferred by the vaccine, the stabilization of BCG potency, optimum dosage and mode of administration.

The present report presents a follow-up study of adolescent children vaccinated with BCG during infancy. The tuberculosis morbidity and mortality, 13 to 24 years after vaccination, should yield information on the duration of immunity.

METHOD OF STUDY

The children comprising this study were vaccinated or followed as controls by the Bureau of Laboratories of the New York City Department of Health between 1926 and 1941. During the course of that investigation over 1000 children were inoculated with BCG vaccine and an approximately equal number were held as controls. Children were referred to the Bureau by tuberculosis hospitals and clinics of New York City. All were originally from tuberculous homes. With few exceptions these children were vaccinated or accepted as controls during the early months following birth and were observed frequently during the first and subsequent years of life. A detailed review of the methods used in that investigation has already been published.[1,2] In 1942, due to the World War and the paucity of nurses, the follow-up study of the children under observation was discontinued.

The study was reactivated in 1946. With the cooperation of the New York City Department of Education, the Public Health Nurses and the Department of Health, it was possible to locate 1165 individuals, adolescent and older, who had been subjects of the original study. Of these, 601 had been vaccinated with BCG during infancy. The remainder, 564, were in the control group. Their ages as of January 1, 1949 are shown in table 1.

Home visits were made on all the subjects by nurses to ascertain their state of health. Roentgenograms were obtained on approximately 550 with the cooperation of the New York City Department of Health. These RGs were read first by Dr. Arthur Robins, Director of the Bureau of Tuberculosis, New York City, and later by Dr. John H. Dale, Jr., Assistant Professor of Pediatrics in Radiology, Cornell University Medical College.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College, New York City.

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A careful study was made of the records of the Bureau of Vital Statistics of New York City for the names of missing children who might have died during the five years from 1942 to 1946 but none were found.

A study of adolescents who had been vaccinated with BCG during infancy raises a number of interesting questions. Since the primary focus of tuberculosis occurs at the site of inoculation with BCG and not in the lungs, the question arises whether in the years

TABLE 1

Age (yr.)	23	22	21	20	19	18	17	16	15	14	13	12	Grand Totals
No. Vacc.	25	54	53	31	35	52	67	72	70	68	57	17	601
No. Cont.	46	21	30	23	75	86	58	49	50	61	49	16	564
Totals	71	75	83	54	110	138	125	121	120	129	106	33	1165

subsequent to the loss of tuberculin sensitivity from BCG (usually 1½ to 2 years) a pulmonary primary complex can occur on exposure to an exogenous tuberculous infection. A further question concerns the fate of the living attenuated bovine bacilli of which the BCG vaccine is composed. Do these organisms remain alive in the body and for how long? If they persist for a period of years, may they return to their former virulence and serve as the source of an endogenous re-infection tuberculosis?

It is important to determine if BCG inoculation causes tissue changes in the vaccinated individual which do not disappear with the disappearance of tuberculin sensitivity.

It is important to ascertain the need for re-vaccination with BCG if the tuberculin sensitivity of vaccinated cases disappears. These and other questions require answers.

Results

Of the 1165 cases re-located and followed in the present study, RGs of the chest were obtained on 584 of which 298 had been vaccinated with BCG during early infancy and 286 held as controls.

Of the vaccinated cases there were three whose chest RGs gave evidence of a healed primary complex. There were also two cases with re-infection tuberculosis. These will be discussed later.

Of 286 controls there were 27 showing definite calcific deposits in the lung fields, evidence of a healed primary complex. There were no cases of re-infection tuberculosis in the control group. (See table 2.)

TABLE 2

Roentgenographic Findings

Groups	No. of Cases	Healed Pulm. 1° Complex	Re-infection TBC
Vaccinated	298	3	2
Controls	286	27	0

If three of the vaccinated cases later developed primary tuberculosis lesions in the lungs, it is a significant finding. A detailed review of their course is therefore indicated in order to appraise such extrinsic factors as a weak or inactive vaccine or an exposure immediately before or immediately after vaccination, where human tubercle bacilli might have become implanted before the vaccine had an opportunity to act.

Case 1. I. D. was born on 2/11/27. She was exposed to a father with a positive sputum from birth to 4 mo. of age, from 5 through 9 mo. of age and from 25 through 28 mo. of age. Intradermal tuberculin tests prior to BCG inoculation were:

11/18/27	at 9 mo.	0.1 mg. —	11/5/28	21 mo.	0.1 mg. —
3/28/28	13 mo.	0.1 mg. +	2/26/29	24 mo.	2.0 mg. —
7/28/28	17 mo.	0.1 mg. —	5/26/29	27 mo.	0.1 mg. —

At 28 mo. of age, the child was vaccinated subcutaneously with 0.01 mg. BCG. Tubercclin test to 0.5 hg. 13 days later showed a positive reaction with an induration of 12 mm. in width. Two weeks later, on 7/3/29, the tuberculin test gave a marked reaction with an induration of 35 mm. in width. Subsequent tuberculin tests to 0.01 mg. were as follows:

8/20/29	at 31 mo. 3+	4/14/31	50 mo. —
1/24/30	36 mo. 3+	5/25/31	52 mo. +
4/8/30	38 mo. 3+	7/13/31	54 mo. —
5/27/30	40 mo. 3+		59 mo. +
1/20/31	47 mo. 3+		67 mo. +
3/11/31	48 mo. 3+		

RGs of the chest were negative on 11/16/27, 3/28/28, 7/18/28, 11/7/28, 2/26/29, 5/17/29 and 6/4/29. The child was vaccinated 2 days later (6/6/29). RG taken on 8/22/29 showed widening of the mediastinum but was otherwise negative. RGs taken on 8/22/29, 10/7/29, 3/27/30, 5/9/30, 4/14/31, 1/1/32, 9/26/32, and 4/26/35 were read as negative by Dr. John Caffey, Roentgenologist and Attending Physician, Babies Hospital, Columbia Medical Center, as well as by the author, although in retrospect one can observe definite hilar calcification in the chest plates of 1/1/32, 9/26/32, 4/26/35. Calcification was clearly evident in the RG of 2/3/47. It is also significant that although the BCG vaccination was given subcutaneously, which usually results in draining sinuses, in this particular case, the local lesion was not seen until 9 mo. after vaccination at which time it was a mere papule of 3 mm. This papule disappeared quickly.

A review of the history of this child suggests the strong possibility that the child had been exposed and infected with human tubercle bacilli immediately prior to vaccination during the pre-allergic phase of the primary complex inasmuch as the tuberculin test following the BCG inoculation was positive 13 days after vaccination. Four weeks after vaccination the tuberculin reaction was marked showing an induration of 35 mm. This degree of tuberculin reaction was maintained for approximately 18 mo. This development of tuberculin sensitivity following vaccination with BCG is unusual since it generally takes 4 to 6 wk. for the tuberculin reaction to become positive following BCG inoculation. Furthermore the degree of the reaction was much more severe than that which usually results from the BCG alone. The fact that the local lesion was so negligible also appears significant. It seems fair to assume, therefore, that in this child, a human infection took seat prior to effective BCG vaccination rather than the occurrence of a primary pulmonary tuberculosis complex subsequent to successful inoculation with BCG.

Case 2. P.S. was born on 8/10/33. He was exposed from birth to 40 mo. of age to his father with negative sputum and exposed occasionally to his father with positive sputum from 40 to 60 mo. of age. An intradermal tuberculin test to 0.2 mg. was negative on 10/24/33 and a test to 10.0 mg. was negative on 11/22/33. Chest RGs were also negative on these dates. On 11/22/33, the child was vaccinated with 0.3 mg. BCG in the thigh. There was some bleeding as well as leakage. The vaccine was 5 days old. Tuberculin tests to 0.1 mg. gave an induration of only 5 mm. on 2/7/34, 2/21/34 and 3/31/34.

Subsequent tuberculin tests gave the following reactions:

5/ 2 /34	1.0 mg.	±	6/ 5 /35		—
8/ 1 /34	0.1 mg.	±	10/ 2 /35		—
10/24/34	10.0 mg.	—	1/ 8 /36	10.0 mg.	—
1/30/35		—	12/11/38		—
2/21/35		—			
2/28/35		—			

RGs on 12/6/33, 3/21/34, 9/12/34, 6/5/35 and 11/20/35 were entirely negative, showing no evidence of mediastinal widening or parenchymal infiltration. It might also be noted that the local lesion from the vaccination never exceeded 3 mm. in width. There was only a slight increase temporarily of the lymph nodes draining the site of vaccination. RG taken on 3/19/48 shows definite calcification of the left hilum with calcification of the left hilar nodes.

In reviewing the history of this subject one is impressed with the possibility that the vaccination lacked its customary potency as judged by the weak tuberculin sensitivity acquired by the skin, and the small size of the local lesion. This may have been due to the fact that there was bleeding as well as leakage at the site of inoculation. It is probable, therefore, that with the loss of the weak tuberculin sensitivity the living tissue once again returned to its pre-allergic condition and that an exogenous tuberculous infection instituted a primary complex similar in every way to what would have been attained had the child not been vaccinated.

Case 3. J.W. was born on 12/6/32. His mother had active tuberculosis with a positive sputum. The child was openly exposed from 6 wk. of age until 7 mo. and from 9 mo. to 10 mo. of age at which time his mother died. The baby was born at Sea View Hospital and 7 tuberculin tests during the 1st 6 wk. of life were negative. At 6 wk. of age, the child was vaccinated intradermally with 0.3 mg. BCG. There was some leakage and a moderate amount of bleeding. The age of the vaccine was 10 days. On 1/21/33, the child was sent to his home where he was exposed to his mother. Subsequent tuberculin tests gave the following reactions to 0.1 mg.:

1/27/33	—	6/12/33	2+
4/25/33	2+		

On 9/27/33, the mother died of tuberculosis.

Tuberculin tests continued as follows:

10/10/33	2+	10/22/35	2+
11/21/33	2+	1/14/36	±
1/ 9/34	1+	7/28/36	±
5/29/34	1+	1/19/37	—
8/25/34	2+	2/18/38	±
4/30/35	1+		

Chest RGs on 2/23/37 showed marked calcification. This is interesting in view of the fact that a tuberculin test on 1/19/37 was negative. The BCG local lesion developed to a papule of 8 mm. and then subsided leaving a scar, 4 mm. in width. The inguinal nodes draining the BCG local lesion were slightly enlarged for most of the first year and then subsided completely.

In reviewing this case several possibilities present themselves. The first is that the BCG, being 10 days old, was weak in potency and also weakened further due to loss by bleeding and leakage, and therefore was not adequate to produce a good degree of immunity against an exogenous infection which occurred later. The second and more probable explanation is that the child was vaccinated and exposed to its mother 1 wk. later, before the vaccine had had a chance to act. RG of the lungs taken on 3/21/47 shows calcification in the same localities as seen on the plates of 1937.

In addition, 2 children who received BCG inoculation developed the re-infection type of tuberculosis in their adolescence. These cases are of particular importance because the question arises whether the re-infection was: (a) an endogenous re-infection of a primary pulmonary human tuberculous infection which occurred in childhood prevaccination or immediately postvaccination before the vaccine had had a chance to act, or postvaccination related to a vaccine of weak potency or inadequate dosage; (b) an endogenous re-infection with bovine tuberculous organisms stemming

from the BCG vaccine and resuming virulence in the course of years within the human host; (c) a re-infection with human tubercle bacilli from an exogenous source, alighting on tissue which had lost its sensitivity to tuberculin; (d) a re-infection with human tubercle bacilli from an endogenous source occurring in tissue which had already been sensitized by human tubercle bacilli rather than by BCG; (e) an exogenous re-infection with human tubercle bacilli, alighting on tissue sensitized by BCG, a theory propounded by Meyers.[3]

Case 4. O. L. was born in 7/7/29. Her mother had active tuberculosis but she was separated from her until 37 mo. of age, July 1932. She was exposed to the mother with positive sputum from 37 to 38 mo. of age and then separated until she was 55 mo. old, February 1934, when the mother returned home with a negative sputum. The child was first seen on 11/13/29 and, after a series of tuberculin tests had all been consistently negative, she was vaccinated on 2/10/30 intradermally with 0.01 mg. BCG. Tuberculin tests to 0.2 mg. tuberculin following vaccination were as follows:

2/19/30	—	1/21/31	±
3/12/30 Chest RG—negative	—	4/ 8/31	2+
3/26/30	±	5/27/31	—
4/23/30	±	9/30/31	+
5/ 7/30	±	12/16/31	±
7/19/30	2+	3/ 2/32	—
7/23/30	±		
11/19/30	—		

It will be noted that up to this time the tuberculin reaction was weak and fluctuating.

In July 1932, when the child was 37 mo. of age, the mother with active tuberculosis and positive sputum returned home and spent 1 full month in direct contact with the child. On 11/16/32, the tuberculin test was 3+ and a tuberculous phlyctenular conjunctivitis was noted. Tuberculin tests to 0.1 mg. continued as follows:

3/ 8/33	3+	* 6/17/34	4+	(blister)
4/20/33	3+	6/19/35	4+	"
11/ 8/33	3+	8/21/35	4+	"
2/25/34	3+	8/12/36	3+	

* 6/17/34, 4+: Phlyctenular conjunctivitis was still present at this time and did not heal completely till 14 mo. later.

Chest RGs taken on 6/19/35 and again on 3/18/36 and 8/12/36 showed calcific masses in both hilar regions. The child appeared generally in good condition although there were scars on the sclera of her eyes. When the patient was 18 yr. of age, she developed a re-infection type tuberculosis with an exudative productive lesion involving the first, second and third interspaces of the right lung. She was treated at a sanitarium but at no time was the sputum positive. At present she is home and is being followed routinely as an arrested case. In this particular case the local lesion from the BCG vaccination was never larger than 4 mm. in width although it did develop a small necrotic center. The inguinal node never enlarged and the local lesion finally disappeared.

One would surmise in reviewing this case that the vaccination took poorly and that what immunity was conferred was weak and of short duration. It would appear that the child at 37 mo. of age received a massive exposure to human tubercle bacilli when the mother returned home with a positive sputum. Undoubtedly a pulmonary primary complex occurred with a hematogenous spread to the eyes. It is difficult to say whether the re-infection discovered in 1947 was exogenous or endogenous in origin.

Case 5. H.W. was born on 10/27/37. She was exposed to a father with a positive sputum from birth to 3 mo. of age, after which her father's sputum became negative. The child was vaccinated at 17 days of age, intradermally with 0.15 mg. BCG in the left thigh. There was no bleeding and very slight oozing. The vaccine was 6 days old.

Subsequent tuberculin reactions to 0.1 mg. were as follows:

12/22/37	2+	9/28/38	2+
3/ 2/38	2+	3/ 8/39	1+
5/25/38	2+	9/ 4/40	—

The patient moved in 1941 and further tuberculin tests were impossible. The local lesion increased until on 1/19/38 it was 8 mm. in diameter and developed a necrotic center. Thereafter it subsided finally leaving a scar 5 mm. x 8 mm. The left inguinal node which drained the site of the BCG vaccination enlarged rapidly and on 12/22/37, 5 wk. after vaccination, had attained a size of a small olive. This node increased in size until on 6/22/38 it had assumed the dimensions of a large olive. Thereafter it subsided gradually and on 6/7/39 was no longer enlarged.

This case undoubtedly received what would be considered as the desired reaction to a BCG vaccination. There was a good local lesion, definite enlarging of the inguinal node, and the development of a positive tuberculin reaction. The tuberculin sensitivity, however, subsided completely within the period of 18 mo. to 3 yr. of age. This patient was followed routinely in the Department of Health Center in New York City. In June 1945, her chest RG was negative. A note was made at this time that there were 5 cases of tuberculosis in the family. A chest RG on 2/18/47 was again negative. Two years later the RG showed evidence of a re-infection tuberculosis with fibrotic change in left apical area and when the sputum was found to be positive the patient was admitted to Seton Hospital. Specimens of this positive sputum were sent to the Public Health Research Institute where they were examined by Dr. Jules Freund in an effort to determine if the organism was one of bovine or human type. The results after inoculation into 4 rabbits indicated that the organism was the human tubercle bacillus. One would conclude therefore that this child received BCG and after approximately 2 yr. lost her sensitivity to tuberculin, and that at a later date, she acquired an exogenous human tuberculous infection with the subsequent formation of the re-infection type tuberculosis.

In reviewing these 5 cases one is impressed with the fact that in all except Case 5 the possibility of inadequate vaccination may have been given during the pre-allergic phase of a human tuberculous infection. Cases 2 and 4 suggest weakness of the vaccine as evidenced by small local lesion and weak tuberculin sensitivity. Case 3 presents the double possibility of weak vaccine as well as exposure to a tuberculous mother immediately after vaccination.

As has been previously stated these 5 cases just reviewed were the only ones showing evidence of a primary pulmonary complex or a pulmonary re-infection tuberculosis among 298 vaccinated cases that had received RGs of the lungs during adolescence.

In contrast, among 286 controls that had received chest RGs, there were 29 with evidence of a healed pulmonary primary complex. There were no cases with re-infection pulmonary tuberculosis.

In reviewing the histories, tuberculin reactions and chest RGs of these 29 controls, it is apparent that 20 of these cases passed through the primary complex while under 5 yr. of age. Five cases developed a primary pulmonary complex after 5 yr. of age, while there were 4 cases where lack of sufficient RGs and tuberculin tests makes an accurate decision as to time of first infection impossible.

Discussion

This study provides no evidence that the BCG vaccine given in infancy diminishes the tuberculosis mortality rate among adolescents and young adults. There were no deaths in the vaccinated or control groups and a study of the records of the Bureau of Vital Statistics of the City of New York failed to bring forth in the death list any names of children who could not be re-contacted and followed.

However, one fact is clearly evident from a review of these cases and that is the almost complete absence of evidence of healed pulmonary primary tuberculosis in children who had been vaccinated in infancy. This finding was not unexpected since the BCG inoculation produces a primary focus at the site of vaccination.

This reduction in positive pulmonary RGs following vaccination was reported by Heimbeck[4] as early as 1928 and repeated in various papers, most recently in a paper by Ferguson[5] on the nurses at Saskatchewan. However, to the author's knowledge in no study thus far published has an attempt been made to differentiate between the pulmonary infiltration of a primary complex and those due to re-infection tuberculosis.

From a roentgenographic point of view the value of BCG should rest on its ability not only to prevent complications and sequelae of primary tuberculosis such as miliary tuberculosis and tubercular meningitis but also to prevent the severe type of re-infection tuber-

culosis, specifically that with the caseous-pneumonic involvement.

But if BCG is capable of preventing the formation of a primary pulmonary tuberculous infiltration, it may be of particular benefit to adolescents and young adults with negative tuberculin reactions, for there is a growing feeling that the progression of the pulmonary primary focus to cavitation is far more frequently found following a primary complex in this upper age group than during infancy and childhood.[6,7]

It would appear from this study that great difficulty would be encountered in determining the true efficacy of BCG unless some method is devised for maintaining the potency of the vaccine, and determining the number of viable organisms inoculated at the time of vaccination.

It has been the author's experience as well as the experience of other workers that the fresher vaccine, that is, vaccine given within five days of its production, not only produced larger local lesions but also caused tuberculin reactions of greater intensity and longer duration than with vaccine over five days old. As a matter of fact there is considerable evidence to show that the number of viable BCG organisms diminish rapidly once the vaccine is in dilution.[8–10] Of the three methods in use throughout the world at the present time, only the intradermal method approaches accuracy. With the oral vaccination used largely in Russia and Brazil, there is no knowledge whatsoever of the number of organisms which pass through the intestinal wall. It is known, however, that a great deal of the vaccine is passed out of the system in the feces. The oral method of vaccination was used originally in the BCG studies in New York City but was discarded when it was shown that less than 60% of those vaccinated developed positive tuberculin reactions as compared to over 90% when vaccinations were performed parenterally.[11] With the multiple puncture method as used by Birkhaug in New York State and Rosenthal in Chicago, again no knowledge of the amount of vaccine inoculated is possible. In both of these methods, needles perforate the skin either through a drop of BCG vaccine (Rosenthal), or through filter paper saturated with BCG vaccine (Birkhaug).

On the basis of the findings presented in this study of 1165 children, it would seem reasonable to suggest re-vaccination if the tuberculin reaction is not positive two months after vaccination. It would also seem advisable to tuberculin test at yearly intervals in order to assure the maintenance of a positive tuberculin reaction—re-vaccinating at any time that the reaction becomes negative.

It is of interest that in the studies of nonexposed, parenterally vaccinated infants in the New York City studies, only 72.8% retained their tuberculin sensitivity within a year after vaccination; 53.4% after 2 years; 49.5% after 3 years; and only 43.7% at the end of 5 years. The present study, however, does not give adequate information to answer the question as to whether, with a stable and potent vaccine, there might be permanent tissue changes which in most instances would protect against an exogenous tuberculous infection. Unfortunately at the present time there is no known method of insuring the stability or potency of BCG. The rapid loss of viability of the BCG organisms in dilution has already been mentioned. It has also been pointed out that the same culture of BCG may change in potency as judged by the severity of local lesion following inoculation.[12]

Summary

This study consists of a follow-up of 1165 adolescent children of whom 601 had been vaccinated with BCG during infancy. The remainder, 564, had been followed from infancy as controls.

Approximately 550 of these cases received roentgenographic examinations which were compared with RGs taken during the first 5 years of life.

As was to have been expected, roentgenographic evidence of healed lesions of primary pulmonary tuberculosis was found much more frequently in the control group than those in the group vaccinated by BCG.

Of the 298 vaccinated cases which received RGs there were three with evidence of a healed pulmonary primary complex. There were also two cases with re-infection tuberculosis of the lungs. Of the 286 controls, there were 27 showing evidence of healed pulmonary primary complex. There were no cases of re-infection tuberculosis in the control group.

A study of the three vaccinated cases which developed evidence of a healed primary pulmonary complex suggests that in two of the cases the BCG vaccine was weak or inadequate while in the third case the child has been exposed and was probably vaccinated in the pre-allergic phase of a human tuberculosis infection. Of the two vaccinated cases that developed signs of a re-infection tuberculosis in adolescence, it is evident in the first case that the allergy following a weak BCG inoculation subsided and the child received a subsequent exposure to open tuberculosis, later with the development of the re-infection tuberculosis. The second case with re-infection tuberculosis showed evidence of having lost the tuberculin allergy approximately three years after inoculation.

As yet no evidence is forthcoming on the ability of BCG vaccine given in infancy to diminish the tuberculosis mortality rate among adolescents and young adults. There were no tuberculosis deaths in either group.

It is evident that the BCG inoculation has the ability to prevent a pulmonary primary tuberculosis, at least during the period of postvaccination tuberculin allergy.

There is no evidence to indicate that BCG given in infancy is capable of preventing re-infection tuberculosis in adolescence. It is yet to be demonstrated that if the post-BCG tuberculin allergy is maintained the re-infection type of tuberculosis will be avoided.

It would appear from this study that there is great difficulty in determining the efficacy of BCG unless some method of maintaining the potency be devised and a standard accurate means of inoculation be used.

It is suggested by this study that the BCG tuberculin sensitivity be maintained by re-vaccination whenever the skin reaction becomes negative.

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SPANISH ABSTRACT

Estudio de un Grupo de Adolescentes Vacunados con BCG Durante la Infancia

Consistio el presente estudio en el exámen periodico de 1165 adolescentes, de los cuales 601 fueron vacunados con BCG durante la infancia, sirviendo los 564 restantes como grupo de control.

Éxamenes radiologicos fueron hechos en aproximadamente 550 de estos adolescentes comparandose los resultados con los obtenidos durantes los primeros cinco años de edad.

Como era de esperarse, evidencia radiografica de lesiones de complejo primario pulmonar cicatrizado fueron encontradas con mas frecuencia en el grupo de control que en el grupo vacunado con BCG.

De 298 casos vacunados, tres demostraron evidencia radiografica de complejo primario pulmonar cicatrizado y dos casos desarrollaron una reinfección tuberculosa pulmonar. En los 286 casos del grupo de control, 27 demostraron evidencia de complejo primario pulmonar cicatrizado. No hubo casos de reinfección tuberculosa en este grupo de control.

En el análisis de los tres casos vacunados con BCG que demostraron evidencia de complejo primario pulmonar cicatrizado se encontró que en dos casos la vacuna de BCG fué de potencia inadecuada y en el tercer caso el niño fué expuesto a una tuberculosis contagiosa y probablemente fué vacunado en la fase pre-alergica de la infección tuberculosa humana. En los dos casos vacunados con BCG que desarrollaron signos de reinfección tuberculosa en la adolescencia, fué evidente que en el primer caso la alergia que siguió la inoculacion desaparecio rapidamente y por lo tanto el paciente desarrollo la tuberculosis de reinfección cuando fue expuesto a una tuberculosis contagiosa. El segundo caso con reinfección tuberculosa demostró evidencia de la perdida completa de la alergia aproximadamente tres años después de la inoculacion con el BCG.

Actualmente no hay evidencia definitiva que demuestre que la vacunacion con BCG durante la infancia disminuya la mortalidad de la tuberculosis en adolescentes y adultos jovenes. En los grupos reportados en este estudio no hubo muertes debidas a la infección tuberculosa.

Es evidente que la inoculacion con el BCG tiene la propiedad de prevenir el desarrollo de una tuberculosis pulmonar primaria, al menos durante el periodo post-vacunal alergico tuberculoso.

No existe evidencia demostrativa de que la vacunacion con el BCG durante la infancia sea capaz de prevenir la reinfección tuberculosa en la adolescencia. Aún queda por demostrarse que si la alergia tuberculosa post-vacunal es mantenida, la reinfeccion tuberculosa puede prevenirse.

Este estudio parece demostrar la gran dificultad en la evaluación de la eficacia de la vacuna BCG y de la necesidad de desarrollar un metodo que garantize el mantenimiento de la potencia de la vacuna y de la exactitud de las inoculaciones.

Los autores sugieren que la alergia tuberculosa obtenida con el BCG sea mantenida con revacunaciones cada vez que la reacción de tuberculina en la piel es negativa.

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DIAGNOSIS OF TRICUSPID ATRESIA OR STENOSIS IN INFANTS

Based Upon a Study of 10 Cases*

By BENJAMIN M. GASUL, M.D., EGBERT H. FELL, M.D., WILLIAM MAVRELIS, M.D., AND RAUL CASAS, M.D.
Chicago

DURING the last four years, out of a material of approximately 500 cases of congenital malformations of the heart which have been studied by the authors, 10 cases of tricuspid atresia or stenosis have been encountered. Most of the patients are extremely ill, cyanotic and dyspneic and they usually die between 3 and 5 months of age.[1] Gasul, Fell, Marino and Davis[2] and Fell, Gasul, Davis and Casas[3] recently reported three extremely cyanotic, desperately ill infants, who were successfully operated on for tricuspid atresia. The youngest of the three was only 7 weeks of age and weighed 3.2 kg.† A study of these cases revealed, however, that some of the patients are not amenable to surgery and that surgical intervention would simply hasten their death. The authors, therefore, believe that cases of tricuspid atresia or stenosis should be divided into two large types, depending upon whether they are amenable to surgery.‡

TYPE I. CASES OF TRICUSPID ATRESIA OR STENOSIS AMENABLE TO SURGERY

Anatomically these patients have the following associated malformations (Figs. 1A and B):

a. An interauricular communication—either a patent foramen ovale or an interauricular septal defect.
b. Hypoplasia or absence of the right ventricle, and
c. hypoplasia or atresia of the pulmonary artery. In addition, they may or may not have
d. a patent ductus arteriosus or an
e. interventricular septal defect or both *d* and *e*.

TYPE II. CASES OF TRICUSPID ATRESIA OR HYPOPLASIA NOT AMENABLE TO SURGERY (Figs. 2A and B):

Anatomically these patients have, in addition to the atresia or hypoplasia, the following associated malformations:

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Read at the Second Pan-American Congress of Pediatrics, Mexico, D. F., Mexico, Nov. 2-5, 1949. (Received for publication April 5, 1950.)

* Since the article went to press, 4 additional patients with tricuspid atresia have been studied by the authors.

† A 19 day old infant weighing 3.2 kg. was operated successfully Nov. 11, 1949, at the Presbyterian Hospital, Chicago.

‡ This classification was first suggested by the authors before the meeting of the Chicago Heart Association held on Feb. 18, 1949, at the University of Illinois School of Medicine, Chicago.

FIG. 1. Type I: (A) Photographs of postmortem specimen from infant 11 mo. old having had pulmonary artery-aorta anastomosis 6 mo. prior to death. Cause of death, confluent bronchopneumonia. Large interauricular septal defect is present. Complete absence of tricuspid valve. There is no communication between right auricle and right ventricle. (B) This illustration shows a marked hypoplasia of right ventricle from which small nonfunctioning pulmonary artery is leading. Left ventricle is markedly hypertrophied.

TABLE 1

Type I. Amenable to Surgery

No.	Age	Cyanosis	Cardiac Findings	Roentgen Findings	ECG	Present Status	Autopsy Findings
1	3 mo.	Present	Systolic murmur, 3rd interspace.	Large left ventricle; diminished vascular pulmonary markings; pulmonary concavity.	Left axis deviation	Died at 3 mo.	Tricuspid stenosis; pulmonary atresia; interauricular septal defect; patent ductus arteriosus; bronchopneumonia.
2	7 wk.	Present	Systolic murmur heard all over pericardium	Same	Same	Died at 7 wk. Toxic enteritis acute.	Tricuspid atresia; pulmonary atresia; interauricular and interventricular septal defects; patent ductus arteriosus.
3	1 day	Present	Not noted	None taken	None taken	Died 24 hr. after delivery.	Tricuspid stenosis; pulmonary atresia; patent foramen ovale and ductus arteriosus; edema of brain.
4	24 days	Present	Systolic murmur over pericardium	Large left ventricle; diminished vascular markings.	Left axis deviation	Died suddenly	Tricuspid stenosis; pulmonary atresia; interauricular septal defect; ductus arteriosus patent; bronchopneumonia.
5	7½ wk.	Present	Systolic murmur, 2nd and 3rd left interspaces.	Same	Left axis deviation	Potts-Smith-Gibson operation at 7½ wk. of age. No cyanosis. Good physical condition.	
6	5 mo.	Present	Systolic murmur, 2nd left interspace	Same	Left axis deviation	Successful Potts-Smith operation. Died 6 mo. later of confluent bronchopneumonia.	Artificial ductus patent; ductus arteriosus closed; tricuspid atresia; interauricular septal defect; no interventricular septal defect.
7	3 mo.	Present	No heart murmur	Same	Left axis deviation	Successful operation. Good physical condition; no cyanosis.	
8	18 mo.	Present	Systolic murmur over pericardium			Successful Blalock-Taussig operation. Good physical condition.	

TABLE 2

Type II. Not Amenable to Surgery

No.	Age	Cyanosis	Cardiac Findings	Roentgen Findings	ECG	Present Status	Autopsy Findings
1	23 mo.	Moderate	Systolic murmur, faint, 4th right parasternal area.	Cardiac shadow enlarged; increased vascular pulmonary markings; large left ventricle.	Left axis deviation	Died at 23 mo.	Tricuspid atresia; transposition of great vessels; patent foramen ovale; interventricular septal defect; double superior vena cava; bronchopneumonia.
2*	2½ mo.	Moderate	Systolic murmur over pericardium.	Heart enlarged; increased vascular pulmonary markings; large left ventricle.	Left axis deviation	Died within 24 hr. after admission.	Tricuspid atresia; complete transposition of great vessels; interventricular septal defect; patent ductus arteriosus.

* Dr. Maurice Lev performed the autopsy on Patient 2, Type II.

FIG. 2. Type II: (A) Postmortem specimen of Type II case showing small right ventricle communicating with left ventricle by interventricular septal defect. Aorta is leading from this hypoplastic right ventricle. There is complete absence of tricuspid valve. This case had 2 superior vena cavae, both entering into right auricle. (B) Left side of heart with hypertrophied left ventricle and interauricular septal defect. Pulmonary artery is coming off this left ventricle. Ductus arteriosus is patent.

a. Interauricular communication.
b. Hypoplasia of the right ventricle, and
c. complete transposition of the great vessels. Because the pulmonary artery originates from the large left ventricle, and the aorta from the hypoplastic right ventricle, the pulmonary artery is usually of larger caliber than the aorta. In addition to these defects, these cases have either
d. an interventricular septal defect or
e. patent ductus arteriosus, or
f. both *d* and *e*.

Eight of the patients reported here belonged to Type I and two to Type II (see tables 1 and 2).

HEMODYNAMICS OF THE TWO TYPES

The hemodynamics in Type I is shown in figure 3. The hemodynamics in Type II is shown in figure 4.

In Type I, venous blood returning from the superior and inferior vena cavae into the right auricle enters the left auricle through the interauricular communication. In case there is a triscuspid stenosis instead of an atresia, a small amount of the venous blood will also enter the right ventricle. The venous blood in the left auricle is mixed with the oxygenated blood that empties into the left auricle from the pulmonary veins. From the left auricle the mixed blood flows into the left ventricle, aorta and out into the systemic circulation. If there is a complete atresia, venous blood can enter the lungs only through

* Dr. Maurice Lev performed the autopsy on Patient 2, Type II.

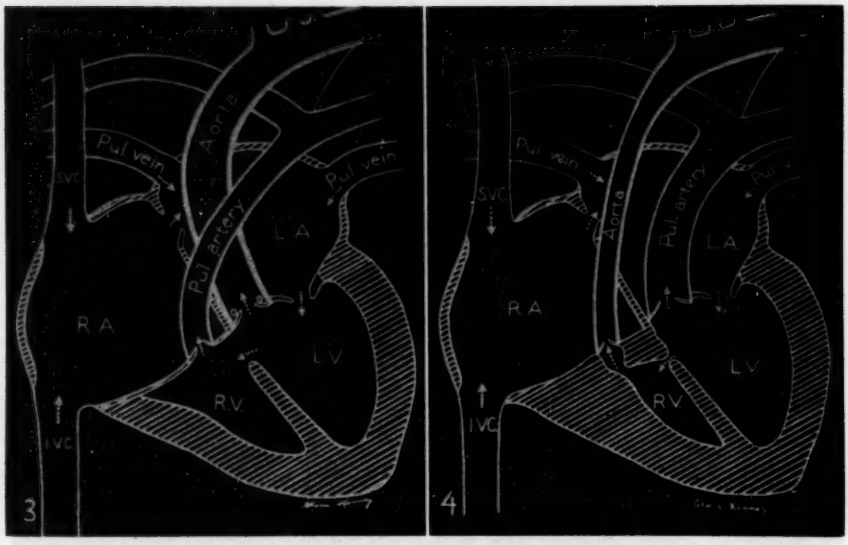


FIG. 3. (Type I) In absence of tricuspid valve blood flows from right auricle into left auricle to left ventricle and aorta. It is difficult for blood to reach lungs; however, if interventricular septal defect is present, hypoplastic right ventricle may pump small amounts of blood into pulmonary artery, or if ductus arteriosus is patent there will be shunt from aorta to pulmonary artery. One or both compensatory mechanisms are essential for life.

FIG. 4. (Type II) In this case there is great difficulty in oxygenated blood's reaching aorta. If interventricular septal defect is present, blood is pumped from right ventricle into aorta. Otherwise patent ductus arteriosus is pathway for pulmonary aortic shunt.

either a patent ductus arteriosus or through an interventricular septal defect. If the pulmonary artery is atresic or the ductus arteriosus closes, life is impossible.

In Type II, venous blood from the vena cavae enters the right auricle, then through the interauricular septal defect into the left auricle, left ventricle, pulmonary artery and back again into the left auricle through the pulmonary veins. The only way life can be maintained is either through a patent ductus arteriosus pumping blood into the aorta, or through an interventricular septal defect into the right ventricle and then into the aorta.

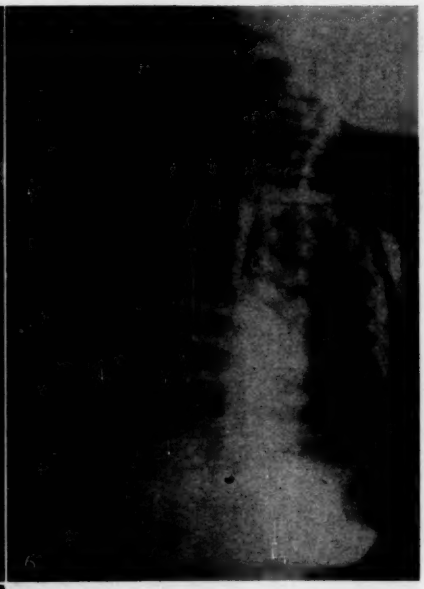
In Type I, there is an insufficient amount of blood entering the pulmonary artery, and in Type II, there is great difficulty in oxygenated blood reaching the aorta.

CLINICAL FINDINGS

The clinical findings in Type I are:

1. Cyanosis usually appears early in life and soon becomes intense. Since one cannot expect to have a normal sized pulmonary artery coming off a hypoplastic or absent right ventricle, there is insufficient blood supply to the lungs and cyanosis becomes more and more pronounced. When the ductus arteriosus closes and there is no interventricular septal defect, the patient dies.

Clubbing of the fingers and toes appears early, and polycythemia with a high hematocrit is proportional to the degree of cyanosis.



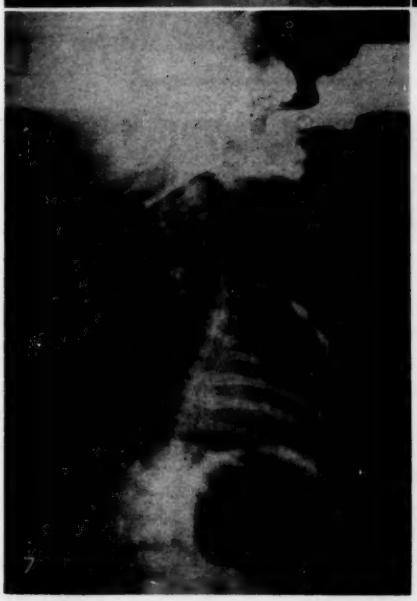


FIG. 5. P. A. view of chest of Case 5 shows concavity in region of pulmonary conus and definite decrease in pulmonary vascular markings, verified by fluoroscopic examination.

FIG. 6. Left anterior oblique view gives (Case 5) evidence of enlargement of left ventricular shadow which extends posteriorly and shows small right ventricle. There is large clear pulmonary window.

FIG. 7. This right anterior oblique view shows concavity in region of pulmonary conus.

2. The heart is usually not much enlarged on percussion. Murmurs may or may not be present, depending upon the presence and size of the interventricular or interauricular septal defects. If they are present, they are systolic in time and usually heard best at the base of the heart. If there is only a patent foramen ovale and no interauricular septal defect present, presystolic pulsation of the liver may be noted.

3. Fluoroscopic and roentgen ray examination of the heart is of extreme importance in diagnosis.

In the anteroposterior position there is a concavity (Fig. 5) in the region of the pulmonary conus and the vascular pulmonary markings are diminished; occasionally one sees very little of the heart shadow to the right of the spinal column.

In the left anterior oblique view, the left ventricle (Fig. 6) occupies most of the cardiac shadow and it takes a great deal of rotation to clear the heart from the spine. The right ventricle is small or absent, as shown by the fact that the anterior portion of

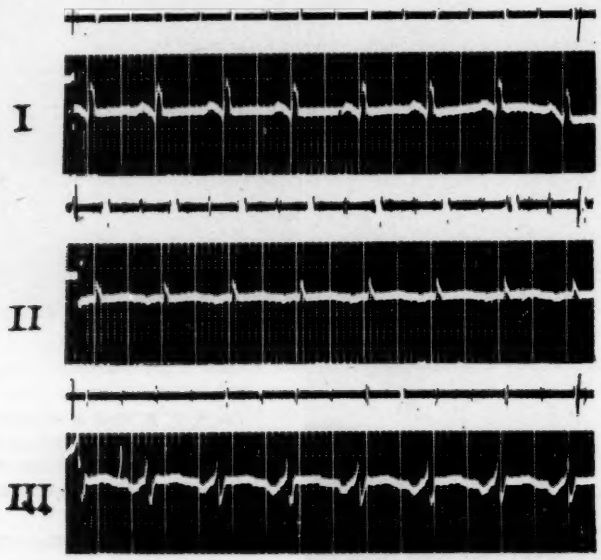


FIG. 8. ECG showing definite abnormal left axis deviation for this group (Case 5).

the cardiac shadow does not extend beyond the shadow cast by the aorta and is far away from the chest wall. The pulmonary window is usually wide and clear.

In the right anterior oblique view (Fig. 7) the concavity of the pulmonary conus is accentuated.

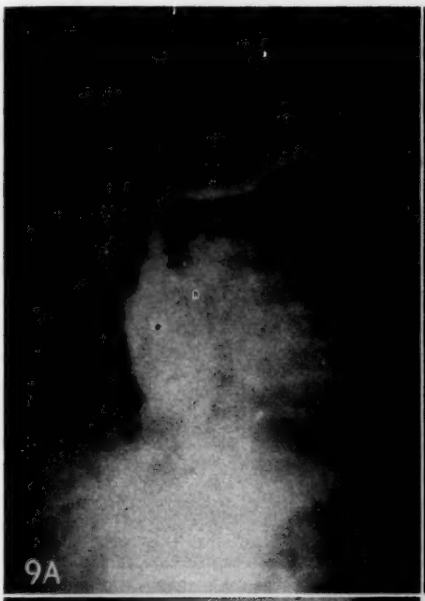
4. The electrocardiogram shows a (Fig. 8) left axis deviation and is of extreme importance in confirming the large size of the left ventricle.

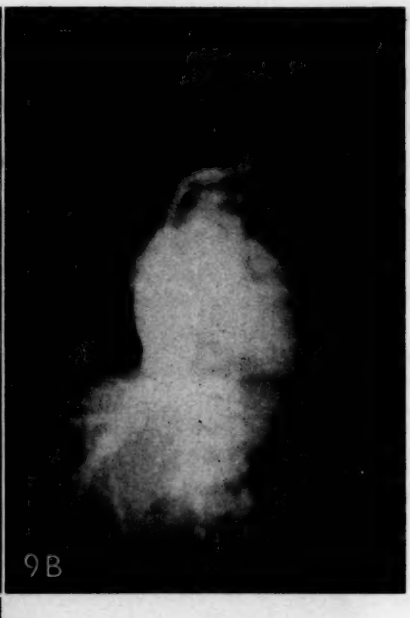
5. The dextroangiocardiogram is a definite help in the diagnosis. This term applied to the visualization of the right heart with contrast medium was first introduced by Dr. A. Castellanos, who taught the authors the technic of angiocardiography. It shows the dye entering the left auricle directly from the right auricle, and the right ventricle cannot be visualized on the first film (Figs. 9A and B).

Since all these cases occurred in young, seriously ill infants, catheterization was not deemed advisable or even necessary and none was, therefore, performed.

The clinical findings in Type II are as follows:

1. Cyanosis, although present, may be less marked, especially if the ductus arteriosus





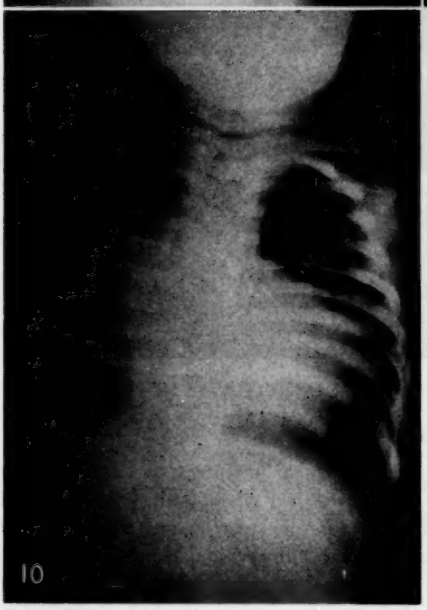


FIG. 9. (A) Film taken 1 sec. after beginning of injection of 15 cc. of 70% diodrast®. Dye is in right auricle and entering left auricle. No visualization of right ventricle with contrast medium. This is diagnostic of tricuspid atresia. (B) Dye is in left ventricle. Right ventricle is not visualized (film 1 sec. after A).

FIG. 10. P. A. RG of chest of patient who has tricuspid atresia with complete transposition of great vessels. Notice definite enlargement of heart and increased vascular markings in lung field. Latter pulsate during fluoroscopic examination.

is patent and the interventricular septal defect is present. The red blood count, the hemoglobin and the hematocrit are proportional to the polycythemia.

2. The heart is usually enlarged; the enlargement is primarily due to the left ventricle. Usually there is also a concavity in the pulmonary conus, but the vascular pulmonary

markings are exaggerated instead of diminished. Since the pulmonary artery originates from the large left ventricle, the lungs are supplied with a great deal of blood, and on fluoroscopic examination, one sees marked vascular pulsations (Fig. 10).

3. The ECG shows a left axis deviation (Fig. 11).

4. The angiocardiogram is similar to that of Type I, except that it shows the pulmonary artery and aorta to be transposed.

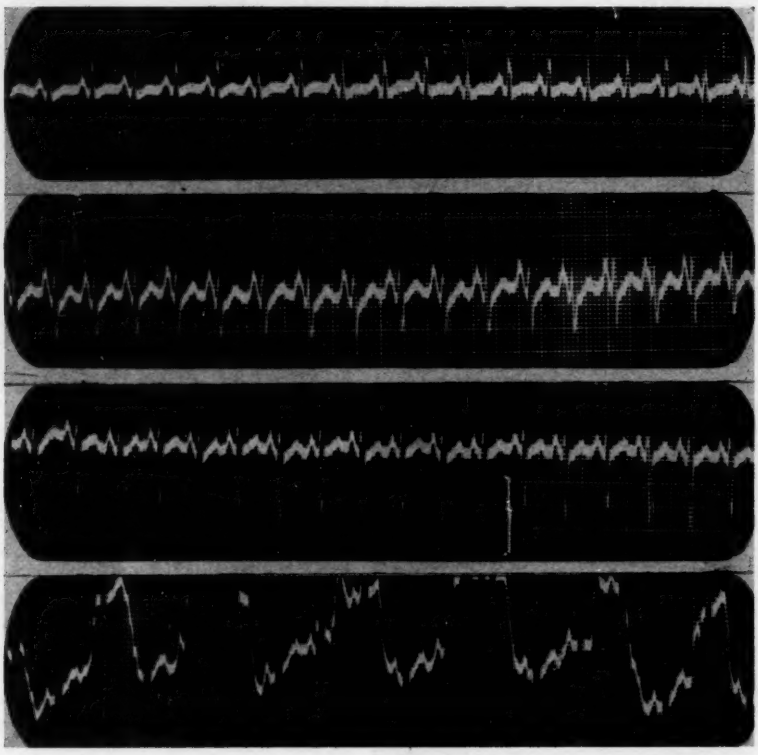


FIG. 11. ECG of same case showing abnormal left axis deviation (Case 1—Type II).

COMMENT

A study of these patients reveals that it is extremely important to make an early diagnosis of tricuspid atresia and to differentiate the two types of this malformation. If left alone, most of these infants die usually before one year of age. The important points in the diagnosis of Type I are: A cyanotic infant with or without a systolic murmur, with the transverse diameter of the heart usually not much enlarged; the pulmonary conus is usually concave and the left ventricle is greatly enlarged; the ECG shows a left axis deviation. The lung fields show diminished vascular markings.

In Type II, the cardiac shadow is usually enlarged and the lung fields show exaggerated vascular pulmonary markings.

In the differential diagnosis consider only cyanotic infants with a left axis deviation. Although it is generally believed that a cyanotic infant with a left axis deviation has a

tricuspid atresia or stenosis,[4] the authors have now encountered three conditions from which tricuspid atresia must be differentiated. Gasul, Richmond and Krakower[5] have reported a case of a cyanotic child whose ECG showed a left heart strain, and the autopsy proved it to be a tetralogy of Fallot with a widely patent foramen ovale (a case of pentology). The only possible way to differentiate clinically this condition from tricuspid atresia is that the transverse diameter of the heart is greatly enlarged and the oblique views show that both ventricles are enlarged. The angiocardiogram will also show a large right ventricle.

The authors have recently studied a 5 month old cyanotic infant with a left axis deviation whose angiocardiogram was perfectly normal and whose cyanosis disappeared completely following the intravenous injection of methylene blue. This patient has a congenital methemaglobinemia and will be reported later in detail.

Two patients are now being studied who were cyanotic during the first 5 or 6 months of life and whose ECGs showed a left axis deviation. The cyanosis has completely disappeared and they are believed to have cases of Ebstein's disease with a patent foramen ovale. These cases will be reported later in detail.

The fourth malformation from which tricuspid atresia must be differentiated is the anomalous entrance of the superior and inferior vena cavae into the left auricle. In the only case reported,[6] the diagnosis was made at autopsy.

Conclusions

Ten cases of tricuspid atresia or stenosis in infants are discussed. A classification of these cases into Type I, amenable to surgery, and Type II, not amenable to surgery, is presented. The clinical, fluoroscopic, roentgenologic, angiocardiographic and electrocardiographic findings in these types are discussed. The differential diagnosis is given briefly.

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Spanish Abstract

El Diagnostico de la Atresia o Estenosis Tricuspidea en Niños Basado en el Estudio de 10 Casos

Los autores estudiaron once casos con atresia y estenosis tricuspidea en niños durantes los últimos cuatro años. Debido a que el tratamiento quirurgico es la indicacion mas importante, los autores clasifican estos casos en dos grupos principales. El grupo I, incluye los casos que presentan una atresia o estenosis de la arteria pulmonar, en los cuales el tratamiento quirurgico está indicado. En el grupo II, se incluyen los casos que no presentan evidencia de atresia o estenosis pulmonar, y en los cuales la cirujia esta contraindicada.

Los autores discuten el cuadro clinico, y los resultados de los examenes fluroscopico, radiografico, electrocardiografico y angiocardiografico obtenidos en ambos grupos.

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STUDIES ON PREMATURITY

II. Influence of Fetal Maturity on Fatality Rate

By MORRIS STEINER, M.D., AND WILLIAM POMERANCE, M.D.

Brooklyn

A SURVEY was made, in a previous paper,[1] of the obstetric problems encountered in the delivery of 962 premature infants born at the Jewish Hospital of Brooklyn during the five year period between 1941 and 1945 inclusive. The bearing of a number of obstetric factors on the survival of these infants was evaluated. Among the conditions studied were the fetal mortality rate in relation to the type of presentation and method of delivery as well as the influence of premature rupture of the membranes on fetal survival. In the present report the data gathered during the five year period have been analyzed in an attempt to determine the significance of fetal maturity as a factor in the survival of 791 infants who were liveborn.

In all previous studies on prematurity infants have been grouped according to birth weight or body length. Peckham[2] has pointed out that these methods of establishing prematurity are grossly inaccurate and suggested that allowances must be made for race, age and parity of mother. He suggested furthermore that separate standards were necessary for single and multiple births. While it is also recognized in a general way that the maturity of an infant at birth is important in its survival, few reports have appeared in which this factor was actually evaluated. Since the present authors' studies took into account the length of the gestation period, it was possible to relate this factor as well as that of birth weight to ultimate survival.

It must be admitted at the outset that the estimation of length of gestation may at times be grossly inaccurate. The reliability of the history regarding the date of the last menses obviously varies with different social groups. In the group reported here 83% were private patients,[1] the vast majority of whom consulted their obstetrician promptly after onset of amenorrhea. It seems likely therefore that the length of the gestation periods recorded in the present study are fairly accurate. Nevertheless, in order to eliminate small errors the cases have been grouped into gestation periods differing from each other by four weeks.

In the analysis of data, babies born of single and multiple births were treated separately. As was pointed out in a previous communication,[1] only babies weighing up to 2250 gm. were included in the study and no exclusions were made on the basis of "non-viability." These criteria had the effect of raising the over-all fatality rate for all babies and especially so for those in the lowest weight class.

The data incorporated in table 1 are presented in such a manner as to take account simultaneously of length of gestation as well as birth weight in relation to survival. Infants were divided into four weight classes and four gestation periods. In the horizontal columns are given fatality rates for the various weight classes within a given gestation period, whereas in the vertical columns are given fatality rates for a given weight class subdivided according to the different lengths of gestation.

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A. Fatality Rates of Babies Born of Single Births

There were 637 babies in the group of single births with 140 deaths, giving an over-all fatality rate of 21.9% (table 1.) For the group with the shortest gestation period (29 weeks or less) the fatality rate was 82.1%; for the group with a gestation period of from 30 to 33 weeks it dropped to 23.5%, while for the group with gestational lengths of from 34 to 37 weeks and from 38 to 40 weeks it fell to 6.4 and 5.7%, respectively. The difference in percentage fatality between the lowest gestation group and the second gestation group is obviously statistically significant. The difference in percentage fatality between the second and third gestation groups is 17.1 ± 2.5. This figure is thus about seven times its probable error and therefore almost certainly significant. One may conclude from the data that the maturity of the infant as measured by varying gestation periods up to 38 weeks played a significant role in its survival.

TABLE 1

Fatality Rate in Relation to Weight and Maturity (Single Births)

Gestation Period	Weight					Total	Per Cent of Total Babies
	Undet.	Less than 1000 gm.	1000 to 1499 gm.	1500 to 1999 gm.	2000 to 2250 gm.		
I. Less than 29 wk.							
No. of Cases	8	52	30	4	1	95	14.9
No. of Deaths	8	51	19	0	0	78	
Per Cent Fatality	100.0	98.1	63.3±5.9	0	0	82.1±2.6	
II. 30–33 wk.							
No. of Cases	2	2	32	94	32	162	25.4
No. of Deaths	2	2	14	18	2	38	
Per Cent Fatality	100.0	100.0	43.8±5.7	19.2	6.3	23.5±2.2	
III. 34–37 wk.							
No. of Cases			14	90	128	232	36.4
No. of Deaths			3	11	1	15	
Per Cent Fatality			21.5±7.2	12.3	0.9	6.4±1.1	
IV. 38–40 wk.							
No. of Cases			3	39	100	142	22.2
No. of Deaths			0	5	3	8	
Per Cent Fatality			0	12.9	3.0	5.7	
V. Unclassified							
No. of Cases				3	3	6	0.93
No. of Deaths				0	1	1	
Per Cent Fatality				0	33.3	16.7	
Total							
No. of Cases	10	54	79	230	264	637	
No. of Deaths	10	53	36	34	7	140	
Per Cent Fatality	100.0	98.2	45.6	14.8	2.6	21.9	
Per Cent of Total Babies	1.5	8.4	12.4	36.1	41.4		

Analysis of the data on the basis of birth weight showed a 98.2% fatality rate for the group of infants weighing less than 1000 gm.; 45.6% for the group weighing from 1000 to 1499 gm.; 14.8% for that between 1500 and 1999 gm.; and 2.6% for that between 2000 and 2250 gm. It will be observed (table 1) that the over-all fatality rate for the 1000 to 1499 gm. weight group was 45.6% but that it varied from 63.3% in the group with shortest gestation to 21.5% in the group with a gestation period from 34 to 37 weeks. The difference in percentage fatality between these two groups is 41.8 ± 9.2, a figure which is about five times as great as its probable error and therefore almost certainly statistically significant. The same relationship, although found in the other weight groups, was less evident because of the generally more favorable outlook for the heavier babies.

TABLE 2

FATALITY RATES IN RELATION TO GESTATION AMONG INFANTS WEIGHING 1000 TO 1499 GM.

Gestation Period	Mean wt.	Median wt.	No. of Cases	Mortality Per Cent
I. Less than 29 wk.	1232 gm.	1162 gm.	30	63.3
II. 30–33 wk.	1340 gm.	1361 gm.	32	43.8
III. 34–37 wk.	1234 gm.	1276 gm.	14	21.5

TABLE 3

FATALITY RATES IN RELATION TO WEIGHT AND MATURITY AMONG INFANTS WEIGHING 1000 TO 1499 GM.

Gestation Period	Less than 29 wk.			30–33 wk.			34–37 wk.		
Wt.	No. Cases	No. Deaths	Fatality Per Cent	No. Cases	No. Deaths	Fatality Per Cent	No. Cases	No. Deaths	Fatality Per Cent
1000–1249 gm.	21	15	71.4	8	5	62.5	6	1	16.7
1250–1499 gm.	9	4	44.5	24	9	37.5	8	2	25.0

The objection may be raised that the lower mortality rate in the older gestational category is merely a reflection of the tendency for the more mature infants to be closely grouped near the highest weight of a given weight class. For this reason the data for infants weighing 1000 to 1499 gm. have been further analyzed to bring out the distribution of cases. In table 2 are listed the mean and median weights for each gestation period. It was indeed found that the mean and median weights in Group II were higher than those for Group I, but that for Group III the figures were again lower so that the mean was practically the same as for Group I. Despite this the mortality rate fell progressively according to gestation period. Additional evidence was obtained by subdivision of this group into two weight classes of 1000 to 1249 gm. and 1250 to 1499 gm. From table 3 it will be seen that in the lower weight group the mortality rate dropped from 71.4% to 16.7% with increasing length of gestation period. This trend was likewise apparent in the higher weight group, though not to as striking a degree. From this table it will also be noted that for a given gestation group the fatality rate varied inversely with the weight of the infant, the heavier infants exhibiting the lower mortality rate. It is thus obvious that there are two factors, weight and maturity, influencing the chance of survival of infants weighing less than 1500 gm.

B. Fatality Rate of Babies Born of Multiple Births

There were 154 babies weighing less than 2250 gm. in the group of multiple births. Of these 16 died, giving an over-all fatality rate of 10.4%, as compared with an over-all fatality rate of 21.9% for babies born of single births. From table 4 it will be seen that only

TABLE 4

Fatality Rate in Relation to Weight and Maturity (Multiple Births)

Gestation Period	Weight				Total	Per Cent of Twin Babies
	Less than 1000 gm.	1000 to 1499 gm.	1500 to 1999 gm.	2000 to 2250 gm.		
I. Less than 29 wk.						
No. of Cases	4	4			8	5.1
No. of Deaths	4	4			8	
Per Cent Fatality	100.0	100.0			100.0	
II. 30–33 wk.						
No. of Cases	1	7	21	3	32	20.7
No. of Deaths	1	2	1	0	4	
Per Cent Fatality	100.0	28.6	4.8	0	12.5	
III. 34–37 wk.						
No. of Cases		1	33	44	78	50.6
No. of Deaths		0	3	1	4	
Per Cent Fatality		0	9.1	2.3	5.2	
IV. 38–40 wk.						
No. of Cases			8	24	32	20.7
No. of Deaths			0	0	0	
Per Cent Fatality			0	0	0	
V. Unclassified						
No. of Cases			1	3	4	2.6
No. of Deaths			0	0	0	
Per Cent Fatality			0	0	0	
Total						
No. of Cases	5	12	63	74	154	
No. of Deaths	5	6	4	1	16	
Per Cent Fatality	100.0	50.0	6.4	5.5	10.4	
Per Cent of Twin Babies	3.2	7.7	40.9	48.0		

25.8% of the babies born of multiple births fell into the two shortest gestation periods, i.e., less than 34 weeks. This figure is to be compared with 40.3% for the infants of single births who had similar gestation periods (table 1). Thus there were fewer babies born of multiple births in the gestational groups where the mortality rate was highest. It is this difference which probably accounts for the lower over-all fatality rate of babies born of multiple births. These findings substantiate the statements of Peckham,[3] and of Dunham and McAlenney.[4]

Although the number of babies in the various gestation periods of the multiple birth

group is small, one notes the same trend for the survival of the infant in relation to its birth weight and gestation period as has been described in the case of single births.

C. Combined Fatality Rate of Babies Born of Single and Multiple Births

In order to facilitate comparison of this data with those in the literature, the combined fatality rates of single and multiple births have been listed in table 5. There was a total of 791 liveborn babies with 156 deaths, giving an over-all fatality rate of 19.8%.

TABLE 5

Fatality Rate in Relation to Weight and Maturity (Single and Multiple Births)

Gestation Period	Weight					Total	Per Cent of Total Premature Babies
	Undet.	Less than 1000 gm.	1000 to 1499 gm.	1500 to 1999 gm.	2000 to 2250 gm.		
I. Less than 29 wk.							
No. of Cases	8	56	34	4	1	103	13.0
No. of Deaths	8	55	23	0	0	86	
Per Cent Fatality	100.0	98.3	67.7	0	0	83.5	
II. 30–33 wk.							
No. of Cases	2	3	39	115	35	194	24.5
No. of Deaths	2	3	16	19	2	42	
Per Cent Fatality	100.0	100.0	41.1	16.6	5.5	22.0	
III. 34–37 wk.							
No. of Cases			15	123	172	310	39.1
No. of Deaths			3	14	2	19	
Per Cent Fatality			20.0	11.4	1.2	6.2	
IV. 38–40 wk.							
No. of Cases			3	47	124	174	21.9
No. of Deaths			0	5	3	8	
Per Cent Fatality			100.0	10.7	2.6	4.6	
V. Unclassified							
No. of Cases				4	6	10	1.2
No. of Deaths				0	1	1	
Per Cent Fatality				0	16.7	10.0	
Total							
No. of Cases	10	59	91	293	338	791	
No. of Deaths	10	58	42	38	8	156	
Per Cent Fatality	100.0	98.4	46.2	13.0	2.4	19.8	
Per Cent of Total Premature Babies	1.2	7.5	11.5	37.1	42.7		

In the gestation period up to 29 weeks the fatality rate was 83.5%; at 30 to 33 weeks it dropped to 22.0% and after 34 weeks it fell to 6.2-4.6%.

Fatality rates based on various weight classes were found to be 98.4% for babies under 1000 gm.; 46.2% for babies in the 1000 to 1499 gm. group; 13.0% in the 1500 to 1999 gm. group and 2.4% in the 2000 to 2250 gm. group. These figures compare favorably

with those given by Dunham[5] for various institutions throughout the country during a similar period. The fatality rate of 2.4% for the 2000 to 2250 gm. group was lower than any in the series cited by Dunham[5] for the weight class of 2000 to 2500 gm. and is the more striking since this group comprised the largest number of infants in this series (338). Moreover it did not include the babies weighing 2250 to 2500 gm., who presumably showed the lowest mortality.

Summary and Conclusions

The fatality rate of 791 liveborn premature infants delivered at the Jewish Hospital of Brooklyn during the five year period from 1941 to 1945 was investigated. The data were analyzed to determine the significance of fetal maturity and of magnitude of birth weight as factors influencing survival.

It was found that for a given weight group, the fatality rate varied inversely with the length of the gestation period. In other words, the outlook for the infant improved in proportion to the degree of its maturity. This was especially striking in the case of infants weighing less than 1500 gm., a result which served to emphasize the importance of length of gestation period as well as birth weight in predicting the chance of survival.

Premature infants born of multiple births had a lower over-all fatality rate than those born of single births. This was directly attributable to the greater maturity of babies born of multiple births.

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Spanish Abstract

Estudios en Prematuros

II. La Influencia de la Madurez Fetal en la Mortalidad

Se investigó el promedio de mortalidad en 791 prematuros (vivos) nacidos en el Jewish Hospital of Brooklyn durante un periodo de cinco años (1941-1945). Estos datos fueron análizados para determinar la significancia de la madurez fetal y la magnitud del peso al nacer como factores determinantes en la sobrevivencia de los prematuros. Se encontró que el promedio de mortalidad en un grupo de prematuros de peso dado, varió inversamente con la duracion del periodo de gestacion. Es decir, que el prognostico es mejor en relacion con el grado de madurez del prematuro. Esto fué especialmente evidente en caso de prematuros que pesaban menos de 1500 gramos. Esto último sirve para destacar la importancia de la duracion del periodo de gestacion y el peso al nacer en determinar las oportunidades de sobrevivencia del prematuro.

Los prematuros nacidos de partos multiples tuvieron una mortalidad promedio menor que los prematuros nacidos de partos sencillos. Esto fue atribuido a la mayor madurez de los niños productos de partos multiples.

555 Prospect Place

CHOICE OF ROOMING-IN OR NEWBORN NURSERY

Analysis of Data from Prenatal Screening Interviews of 1251 Mothers, Relating to Their Choice of Hospital Accommodation for Their Infants in a Rooming-In Unit or in the Newborn Nursery

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AN EXPERIMENTAL Rooming-In Unit for housing together four mother-baby couples was opened at the Grace-New Haven Community Hospital (University Service) in October 1946. The administrative organization of the Unit and its modifications of hospital procedure have been described in detail elsewhere.[1-3] The present paper is a report on one aspect of the pediatric procedures of the Rooming-In Project which relate to the research program being conducted at the Yale University School of Medicine.

The Unit is housed in the former solarium of the maternity ward and was primarily designed for ward and semiprivate patients admitted through the obstetric clinic, but a limited number of patients having private obstetricians and pediatricians are also admitted. The general plan of study calls for interviewing patients in the prenatal clinic by the pediatricians supervising the Unit to determine the mothers' accommodation preference, and interviewing private patient applicants by special appointment. Since applications from private patients are made only by those desiring rooming-in, and because the Unit functions under an allotment system for such patients and applications are not encouraged, the private patients interviewed do not represent an unbiased sample of the possible private patient population of the New Haven Hospital area. In contrast, it has been possible to interview the total population of mothers attending clinic. It was planned that the initial interview with the mother would serve as a basis not only for selection of mothers to fill the Unit, but as a survey of the population of the obstetric clinic which would furnish a basis for evaluating some aspects of the research program.

The present paper is based primarily on an analysis of the first or "screening" interview with mothers registered in obstetric clinic from July 1, 1947 to July 1, 1949. Because of limitations of personnel it was not possible to interview all mothers during the first few months of the Unit's function, but during the two year period covered by this report an attempt was made to interview all patients as to their preference for hospital accommodation. The success of this effort can be judged from the fact that of the

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From the Rooming-In Project, Departments of Pediatrics, Obstetrics, Nursing Education, and Hospital Administration, Yale University School of Medicine, New Haven, Conn., which is supported (in part) by a research grant from the National Institute of Mental Health, U. S. Public Health Service.

The data on which this paper is based was collected by the following pediatric fellows who have worked on the Rooming-In Project: Richard W. Olmsted, M.D.; James A. Kleeman, M.D.; Ruth I. Svibergson, M.D.; George R. Barnes, M.D.; Anton N. Lethin, M.D., and Morris A. Wessel, M.D.

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mothers delivered during 18 months of this period, 77% were seen prenatally by the pediatric fellows of the Rooming-In research staff. An estimated additional 12% of mothers delivered each year are unregistered in the clinic. Data on the small sample of private patients will be presented, but not subjected to statistical analysis. Attendance at obstetric clinic of the New Haven Hospital is regulated by the Admitting Office of the Hospital, and is limited in terms of the family income.* However, although the group attending clinic is primarily constituted of families of lower economic levels, it is somewhat atypical because of the presence of Yale University and other colleges in the Hospital area. That is, wives of undergraduate and graduate students in these colleges fall within the maximum economic level of the clinic, though their socio-educational status differs considerably from that of the typical clinic client.

It is recognized that, during the years which have elapsed since the opening of the Unit, several changes have occurred which may have affected the type of patient attending obstetric clinic, or which may have influenced the mother's accommodation choice. Most outstanding of these are the obstetric plan for handling deliveries through "natural childbirth," the increased community awareness of the Rooming-In Unit, and the opening of a second four-bed Rooming-In Unit in October 1948. This latter brought about a change in the criterion for selection. Prior to the opening of the second Unit, only those mothers were selected for rooming-in who not only desired to have the baby with them but also wished to breast feed. A definite attempt was made to prevent the criterion of breast feeding from becoming known in clinic, in order not to influence the patients' responses to the screening interview. The number of mothers wishing rooming-in and bottle feeding suggests that this attempt was successful. This criterion was dropped on the opening of the second Unit. The possible effect of such changes will be taken into account in the statistical analysis which follows.

The purpose of the screening interview is to obtain basic identification data on the patient, and to determine whether any relationship exists between her preference for rooming-in and certain other variables. This information is secured through recording of the patients' responses to a standardized but flexible interview technic. All interviews are taken as soon as possible after the first obstetric appointment, which varies from the third to eighth month of gestation. The interviews are conducted by pediatricians on the Rooming-In Staff, and are timed so as not to interfere with the routines in the prenatal clinic. Approximately the following form of introduction and explanation of the interview has been used:

"How do you do, Mrs. ————. I'm Dr. ————. I'm one of the doctors who will take care of your baby after it's born. We're interested in the baby, and this gives us a chance to get to know you before the baby comes. It gives us an opportunity to ask you some questions and for you to ask us any questions you may have about the baby."

The interviews are conducted in an unhurried nondirective manner. An indication of the mothers' rapport with the pediatrician is their willingness to remain after the obstetric examination for repeated interviews.

Although modifications have been introduced from time to time, the interview used has been essentially as follows:

* The upper limit for clinic attendance is approximately $2,500 in yearly income, but this limit may be increased up to $5,000 depending on family size and financial burden.

SCREENING INTERVIEW FOR ROOMING-IN STUDY

NAME: AGE: E.D.C.: UNIT NO.:

ADDRESS: PHONE:

How long do you plan to live in New Haven?

GRAVIDA: PARA: ABORTUS: DEATHS:

SEROLOGY: Rh: COLOR: RELIGION (Denom.):

BIRTHPLACE (Your own):

Your Mother's: Your Father's:

" MaGM: " PaGM:

" MaGF: " PaGF:

OCCUPATION OF YOUR FATHER:

YOUR HUSBAND'S AGE: COLOR: RELIGION (Denom.):

BIRTHPLACE (Your husband):

His Mother: His Father:

" MaGM: " PaGM:

" MaGF: " PaGF:

OCCUPATION OF YOUR HUSBAND'S FATHER:

Where did you go to school? How far? Year of graduation:

Your husband's school? How far? Year of graduation:

What kind of work have you done? (Include present occupation)

What is your husband's work? (Past and present)

When were you married? (Verbatim answer, and ask date if not given)

How do you feel about having this baby?

Was the baby planned, or did it just come?

Are you planning to nurse or bottle feed the baby? Why?

In our experience, we have found that some women prefer to have their baby in the room with them in the hospital, and other women would rather have their babies in the nursery and brought to them at regular feeding hours. Which would you prefer? Why?

(If patient has heard of Rooming-In) Where did you hear of it?

INTERVIEWER'S EVALUATION AND REMARKS:

Is this person a good Rooming-In candidate?

If not, give reasons why: (Specify reasons in detail)

INTERVIEWER: _____

DATE: _____

From this interview, the following factors were selected for analysis in relation to accommodation preference: patient's preference in feeding; patient's parity; patient's age; occupation of patient's husband; patient's education; patient's descent;* patient's religion; patient's race.

In the two year period between July 1, 1947 and July 1, 1949, 1251 obstetric clinic patients were interviewed. On the basis of answers to the question as to whether they preferred "to have their baby in the room with them" or "to have their baby in the Nursery," patients were classified into three categories: Rooming-In, where the patient stated a definite preference for having the baby with her; Nursery, where the patient

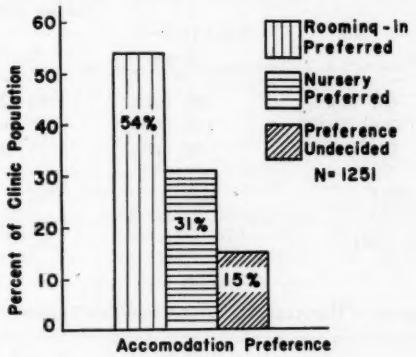

CHART 1. Showing per cent of obstetric clinic population per accommodation preference.

stated a definite preference for having the baby in the separate nursery; and Undecided, where the patient had no definite preference for either accommodation, or expressed herself as indifferent. The percentage of each choice in the total of 1251 cases is shown in chart 1.

In evaluating the following data, it should be kept in mind that the relationship between accommodation preference and the various factors analyzed below is not necessarily representative of the pattern of these factors among mothers actually accommodated in the Rooming-In Unit, but of the pattern at the time of the mother's initial prenatal choice. In particular, it is obvious that shifts to preference for one accommodation or the other of necessity occurred in the Undecided group. In order to have some evaluation of the extent to which shifts among this group might alter the obtained relationships presented here, the data for each variable were analyzed in two ways. Chi-square was computed for the relationship between the various factors and the three accommodation choices, and chi-square was computed for the relationship between the various factors and the division of patients into the dichotomy of preference for Rooming-In and Other (Nursery plus Undecided). It was felt that this latter two-part analysis would give the clearest contrast between those mothers who definitely preferred Rooming-In, and the rest of the clinic population. None of the probability values for the tri-partite chi-squares

* This item varied most in type of information recorded. From July 1947 to July 1948, the mothers were asked their birthplace and descent, generation unspecified; from July 1948 to July 1949, the mothers were asked nationality of parents and grandparents.

differed from those of the bi-partite analysis, and so the latter figures are not included in the present report.*

In evaluating the factors which might influence the mother's choice of hospital accommodation, her feeding preference, parity and age were considered of basic importance. The distribution of accommodation preference in relation to feeding preference is presented in table 1. The feeding preference responses could all be classified as breast, bottle

TABLE 1

PREFERENCE IN HOSPITAL ACCOMMODATION AND PREFERENCE IN FEEDING

Accommodation Preference	No.	Feeding Preference		
		Breast	Bottle	Undecided
Rooming-In	681 (100%)	438 (64%)	194 (29%)	49 (7%)
Nursery	394 (100%)	138 (35%)	235 (60%)	21 (5%)
Undecided	176 (100%)	83 (47%)	76 (43%)	17 (10%)
Total	1251	659	505	87

Chi-square: 102.98, $p: < .001$.

TABLE 2

PREFERENCE IN HOSPITAL ACCOMMODATION AND PATIENT'S PARITY

Accommodation Preference	No.	Parity			
		Primipara	Single Multipara	Multipara	Grand Multipara
Rooming-In	681 (100%)	314 (46%)	198 (29%)	140 (21%)	29 (4%)
Nursery	394 (100%)	96 (24%)	118 (30%)	144 (37%)	36 (9%)
Undecided	176 (100%)	56 (32%)	49 (28%)	55 (31%)	16 (9%)
Total	1251	466	365	339	81

Chi-square: 66.87, $p: < .001$.

and undecided. It will be noted that a highly significant difference† was found between the three groups in feeding preference. The majority of the Rooming-In group prefer breast feeding, while the majority of the Nursery group prefer bottle feeding. The Undecided group is about equally divided on this choice.

Table 2 shows the distribution of accommodation preference in relation to patient's

* In the classification of some of the various factors analyzed, categories occurred containing very small frequencies. These are presented in the tables, but are combined or omitted in the statistical analyses because of the invalidity of calculating chi-square for distributions containing cells with theoretic frequencies under five. It was felt that for the present study, omission or combination of such categories which did not play a major part in the composition of the clinic population would not influence any generalizations to be drawn from the data, while inclusion of them singly might make an erroneous contribution to chi-square.

† For purposes of this study a probability value of $< .05$ was considered indicative of a significant difference, of $< .001$ as highly significant.

parity. For purposes of this analysis, the parity categories were defined as follows: Primipara—no living children; Single Multipara—one living child; Multipara—two, three or four living children; Grand Multipara—five or more living children. It will be noted from the table that there is a highly significant difference in the composition of the groups. As would be anticipated, there is a very small percentage of Grand Multipara in each group. However, while the Undecided group is composed about equally of the three remaining categories, the Rooming-In and Nursery groups show opposing trends. The Primipara constitute the largest percentage of the Rooming-In group, with Single Multipara and Multipara next, in that order. However, the Multipara constitute the largest percentage of the Nursery group, with Single Multipara and Primipara next, in that order. On the whole, the Rooming-In group members have lower parities than the Nursery group members.

TABLE 3

PREFERENCE IN HOSPITAL ACCOMMODATION AND PATIENT'S AGE

Accommodation Preference	No.	Age Range (yr.)				
		–20	21–25	26–30	31–35	36–
Rooming-In	676 (100%)	113 (17%)	248 (36%)	187 (28%)	80 (12%)	48 (7%)
Nursery	388 (100%)	55 (14%)	126 (32%)	119 (31%)	61 (16%)	27 (7%)
Undecided	176 (100%)	27 (15%)	54 (31%)	55 (31%)	25 (14%)	15 (9%)
Total*	1240	195	428	361	166	90

Chi-square: 6.45, p: $< .70 > .50$.

* Age of 11 patients (1%) unknown.

Table 3 presents the relationship between accommodation preference and patient's age. It indicates that age is not a factor in influencing choice, as the three groups are very similar in age composition. This correspondence between the three groups is of interest, as a positive relationship was found between age and parity.* Since a highly significant difference occurs between the groups in parity composition, but not in age composition, it appears that parity is the more important variable in determining mother's preference.

In the cluster of variables which reflect the patient's cultural and economic position are included occupation of patient's husband, and patient's education, religion, descent and race. The relationship between these and mother's accommodation preference will be presented in tables 4 to 8.

In grouping the occupation of patient's husband, as presented in table 4, the classifications of the United States census were used. This aspect of the data of the screening interview was not obtained in sufficient detail to warrant a division into more than five categories. Because of the peculiar composition of the obstetric clinic, previously discussed, the occupation of "student" was added to the conventional ones. The categories used were: Student; Professional; Small Business and Managerial; White Collar; Skilled and

* The contingency coefficient computed was found to be .51.

TABLE 4

PREFERENCE IN HOSPITAL ACCOMMODATION AND OCCUPATION OF PATIENT'S HUSBAND

Accommodation Preference	No.	Occupational Classification*					
		Student	Professional	Small Business	White Collar	Skilled	Unskilled
Rooming-In	642 (100%)	121 (19%)	18 (3%)	11 (2%)	45 (7%)	246 (38%)	201 (31%)
Nursery	378 (100%)	8 (2%)	5 (1%)	8 (2%)	32 (9%)	148 (39%)	177 (47%)
Undecided	166 (100%)	11 (6%)	2 (1%)	1 (1%)	16 (10%)	70 (42%)	66 (40%)
Total†	1186	140	25	20	93	464	444

Chi-square: 77.99, $p.: <.001$.

* For purposes of statistical analysis, the classifications "professional" and "small business" were grouped together.
† Occupation of patient's husband in 65 cases (5%) unknown.

Semi-skilled; Unskilled and Laborer. With few exceptions, the "students" so designated were members of the graduate schools of Yale University, and can also be considered as potential members of the professional group. It will be noted from the table that the preponderance of student wives preferred rooming-in. A highly significant difference was found in the composition of the three groups with respect to husband's occupation. However, the influence of the student group in this classification is apparent if it is omitted from the table. The chi-square value then obtained is 10.75, $p. <.30>.20$. Thus, when the total obstetric clinic population is considered, the three groups show a highly significant difference in type of husband's occupation, but if the atypical student classification is omitted, the groups are fairly similar.

The extent to which inclusion of this student group affects other variables cannot be estimated, as the wives of the students are not represented in a single category. The relationship most likely to be affected is that between accommodation preference and patient's education, as the education of husband and wife tend to be correlated. As presented in table 5, the mothers were classified according to last completed grade, groupings being: zero through eighth grade; ninth through eleventh grade; high school graduation, including additional schooling not college; first through third year college; college graduation; and schooling beyond college graduation. The three groups show a highly significant difference in composition. There is a trend for Rooming-In to be

TABLE 5

PREFERENCE IN HOSPITAL ACCOMMODATION AND PATIENT'S EDUCATION

Accommodation Preference	No.	Educational Classification*					
		Grade 0–8	Grade 9–11	High School Graduation	College 1–3	College Graduation	Post College
Rooming-In	669 (100%)	145 (23%)	221 (33%)	170 (25%)	36 (5%)	80 (12%)	16 (2%)
Nursery	386 (100%)	100 (26%)	174 (45%)	98 (25%)	12 (3%)	2 (1%)	0
Undecided	174 (100%)	57 (33%)	62 (35%)	40 (23%)	7 (4%)	7 (4%)	1 (1%)
Total†	1228	302	457	308	55	89	17

Chi-square: 91.61, $p.<.001$.

* For purposes of statistical analysis, classifications "college graduation" and "post-college" were grouped together.
† Education of 23 patients (2%) unknown.

TABLE 6

PREFERENCE IN HOSPITAL ACCOMMODATION AND PATIENT'S DESCENT

Accommodation Preference	No.	Descent			
		United States	British Isles, N.W. Europe	Southern Europe	Other
Rooming-In	337 (100%)	202 (60%)	34 (10%)	63 (19%)	38 (11%)
Nursery	181 (100%)	102 (56%)	9 (5%)	52 (29%)	18 (10%)
Undecided	70 (100%)	39 (56%)	7 (10%)	21 (30%)	3 (4%)
Total	588	343	50	136	59

Chi-Square: 11.30, p.<.10>.05.

chosen by the higher educated, and Nursery by the less well educated; the Undecided group resembles the Nursery group in this respect. If the educational distribution is divided into High School and below, and College and above, 19% of the Rooming-In group fall into the College and above classification, as compared to 4% of the Nursery group.

Table 6, showing the relation between accommodation preference and patient's descent, is based on the obstetric population for the year July 1, 1948 to July 1, 1949, as this information was not obtained in comparable form for the preceding year. For the distribution according to descent, the data were grouped into the following categories: United States; British Isles and Dominions, and Northwest Europe; Southern Europe; and Other. Table 6 shows no statistically significant relationship between accommodation preference and patient's descent, though there is a tendency for the Rooming-In group to be chosen more often by patients of United States, British Isles, and Northwest European descent, while the Nursery group is chosen more often by people of Southern European descent.

Table 7 shows the relationship between patient's accommodation preference and religion. Religion was classified as Protestant; Catholic; Jewish; and Other, including

TABLE 7

PREFERENCE IN HOSPITAL ACCOMMODATION AND PATIENT'S RELIGION

Accommodation Preference	No.	Religion*			
		Protestant	Catholic	Jewish	Other
Rooming-In	652 (100%)	303 (46%)	324 (50%)	15 (2%)	10 (2%)
Nursery	377 (100%)	154 (41%)	212 (56%)	7 (2%)	4 (1%)
Undecided	166 (100%)	78 (47%)	86 (52%)	0	2 (1%)
Total†	1195	535	622	22	16

Chi-square: 5.47. p.<.20>.20.

* For purposes of statistical analysis, the "Jewish" and "Other" classifications were grouped together.
† Religion of 56 patients (4%) unknown.

patients who specified no particular affiliation. This table shows no significant difference among the three groups with respect to religious classification.

The distribution of accommodation preference according to race is presented in table 8. The table shows a highly significant difference in the composition of the three groups. The Rooming-In group contained a smaller percentage of Negro mothers in proportion to the white mothers than would be expected by chance.

In order to determine whether any trends evident in the data were consistent for the two years, the data were analyzed for each of the two years separately, both according to three category and Rooming-In versus Other (Nursery plus Undecided) comparisons. No shift in significance of results was obtained.

The population analysis just presented is based on the total attendance at obstetric clinic from July 1947 to July 1949. During this period, a limited number of private

TABLE 8

PREFERENCE IN HOSPITAL ACCOMMODATION AND PATIENT'S RACE

Accommodation Preference	No.	Race*		
		White	Negro	Other
Rooming-In	679 (100%)	566 (83%)	109 (16%)	4 (1%)
Nursery	392 (100%)	285 (73%)	107 (27%)	0
Undecided	176 (100%)	121 (69%)	55 (31%)	0
Total†	1247	972	271	4

Chi-square: 28.88, $p. < .001$.

* For purposes of statistical analysis, the "Other" classification was omitted.

† Race of 4 patients (0.2%) unknown.

patients were admitted to the Rooming-In Unit, under various quota allotments during the two years. As previously explained, this group was not an unbiased sample of the possible private patient population of the New Haven Hospital area, but consisted only of quota applications for each month of patients wanting rooming-in. Therefore, the screening interviews for this group were not included in statistical analysis with the clinic screening interviews. The composition of this group, constituting 280 patients, with respect to the various variables is presented in chart 2, together with a composite picture of the clinic patients preferring rooming-in.

Chart 2 therefore represents graphically the composition of the clinic and private groups of patients preferring rooming-in on initial contact. Comparison of the two groups is of interest on several points. The group of private patients differs somewhat in husband's occupation and patient's education, race and religion. That is, the husband in general belongs to a higher professional group, while the patient tends to have more education and more frequently to be of the white race and Protestant religion. The ethnic composition of the groups is fairly similar. In considering basic identification data, it will be noted that the two groups are quite similar in parity and age composition. The most marked divergence is in feeding preference, in that a larger percentage of private patients preferred breast feeding. Whether this was a reflection of knowledge

among this group of the criterion for admission to Rooming-In, or reflects a more basic cultural difference, remains to be determined.

SUMMARY

From July 1, 1947 to July 1, 1949, 1251 mothers attending the obstetric clinic of the University Service of the Grace-New Haven Community Hospital were "screened"

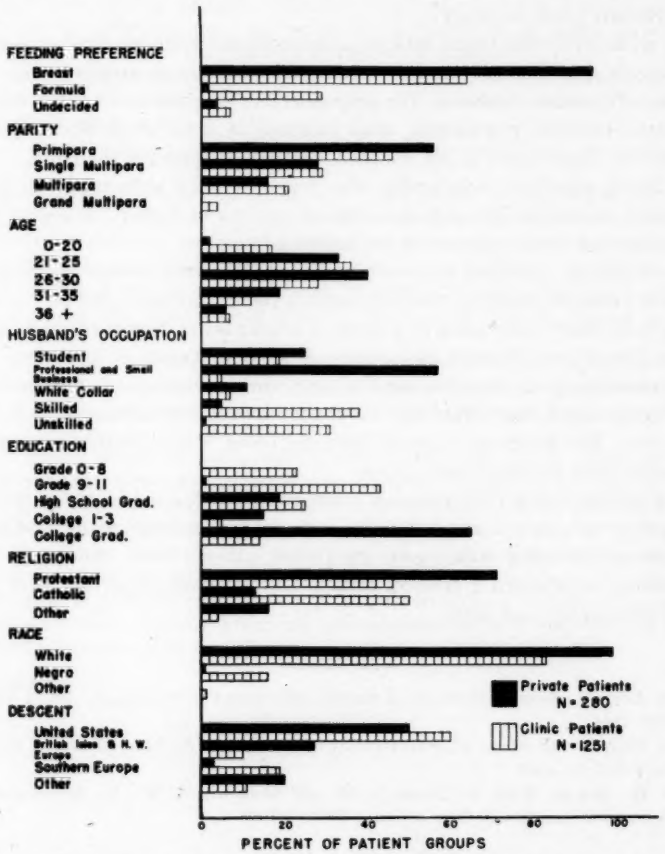

CHART 2. Showing composition of patient groups preferring rooming-in at time of screening interview.

through interview to determine their preference in hospital accommodation and to obtain basic identification data. Patients were grouped according to preference for Rooming-In, preference for Nursery, and Undecided. The significance of the relationship between accommodation preference and patient's feeding preference, parity, age, education, descent, religion, race and occupation of patient's husband was then statistically determined. It was found that inclusion of the Undecided group with the Nursery group did not alter the statistical significance of any of the obtained relationships, and conse-

quently only the Rooming-In and Nursery groups will be contrasted in the following summary:

1. A highly significant relationship was found between accommodation preference and feeding preference. The majority of the Rooming-In group preferred breast feeding, the majority of the Nursery group preferred bottle feeding.

2. A highly significant relationship was found between accommodation preference and patient's parity. On the whole, the Rooming-In group members have lower parities than the Nursery group members.

3. No relationship was found between accommodation preference and patient's age.

4. A highly significant relationship was found between accommodation preference and occupation of patient's husband. The preponderance of patients in upper occupational classifications (student, professional, small business) occurred in the Rooming-In group. If the student classification is not included, the groups approach similarity.

5. A highly significant relationship was found between accommodation preference and patient's education. The preponderance of patients in higher educational classifications (college and above) occurred in the Rooming-In group.

6. No statistically significant relationship was found between accommodation preference and patient's descent, though a trend approaching significance was noted for the Rooming-In group to be chosen more often by patients of United States, British Isles, and Northwest European descent, and Nursery by patients of Southern European descent.

7. No relationship was found between accommodation preference and patient's religion.

8. A highly significant relationship was found between accommodation preference and patient's race. The Rooming-In group contained fewer Negro mothers in proportion to white mothers than did the Nursery group.

During the two year period, screening interviews were obtained on 280 private patients. As this group was a biased sample, the data were not analyzed statistically. Compared with clinic patients preferring rooming-in, the private patients more consistently preferred breast feeding, represented a different cultural and economic group, but were similar to the clinic group in age and parity.

References

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Spanish Abstract

Seleccion de Acomodacion Combinada de Madre e Hijo o de Acomodacion del Hijo en la Sala de Recién Nacidos

Análisis de los Resultados Obtenidos durante la Entrevista Pre-natal de 1251 Madres, y de la Preferencia de Acomodacion Hospitalaria Deseada para los Hijos

Durante el periodo de Julio 1, 1947 a Julio 1, 1949, un total de 1251 madres atendidas en la consulta externa obstetrica universitaria del Grace-New Haven Community Hospital fueron entrevistadas a fin de determinar el tipo de acomodacion hospitalaria preferida y además obtener otros datos de identificacion personal. Los pacientes fueron agrupados de la manera siguiente: a.) el

grupo de madres que prefirieron la acomodacion combinada con el hijo (Rooming-in); b.) el grupo de madres que prefirieron mantener al hijo en la sala de recién nacidos; y c.) el grupo de madres sin preferencia determinada.

Se determinó estadisticamente la significancia de la correlacion entre la acomodacion y el tipo de alimentacion preferida, número de embarazos, la edad, educacion, descendencia, religion, raza y ocupacion del esposo. Pudo determinarse que la adición de las madres del grupo (c) al grupo (b) no alteró los resultados estadisticos de ninguna de las correlaciones obtenidas, por consiguiente la siguiente comparacion solo se hace entre los dos grupos primeros.

1. Se observo una relacion significativa entre el tipo de acomodacion y la alimentacion preferida. La mayoria de las madres del grupo (a) prefirieron la alimentacion al pecho, mientras que la mayoria de las madres del grupo (b) prefirieron la alimentacion artificial.

2. Una relacion tambien significativa se observó entre la preferencia de acomodacion y el número de embarazos de la madre. Por lo general las madres pertenecientes al grupo (a) tenian menor numero de embarazos que las del grupo (b).

3. No se observó ninguna correlacion importante entre la preferencia de acomodacion y la edad de la madre.

4. Se encontró una correlacion significativa entre la preferencia de acomodacion y la ocupacion del esposo. El grupo (a) fué altamente favorecido por las madres pertenecientes a esferas ocupacionales elevadas (estudiantes, profesionales, pequeños comerciantes). Si la clase estudiante no se incluye los grupos a y b resultan similares.

5. No se encontró correlacion importante entre la preferencia de acomodacion y la educacion de la madre. Se observó una preponderancia de madres pertenecientes a niveles elevados de educacion en el grupo (a).

6. No hubo ninguna relacion estadistica de importancia entre la acomodacion preferida y la descendencia de la madre, aunque se observo una ligera inclinacion por las madres descendientes de Estados Unidos, Inglaterra y noroeste de Europa por el grupo (a), mientras que el grupo (b) fué favorecido por las madres descendientes del sur de Europa.

7. No se observó correlacion alguna entre la acomodacion preferida y la religion del paciente.

8. Se observó una correlacion significativa entre el tipo de acomodacion y la raza del paciente. El grupo (a) fué menos favorecido por las madres de la raza negra, las cuales prefirieron el tipo de acomodacion separada del grupo (b).

Similarmente, durante un periodo de dos años un grupo de 280 pacientes privados fueron entrevistados pero los cuales no fueron analizados estadisticamente. Las madres de este último grupo que prefirieron la acomodacion combinada del grupo (a) favorecieron también la alimentacion al pecho. Aunque este último grupo fue diferente al anterior desde el punto de vista economico y cultural, la edad y numero de embarazos de las madres fueron similares.

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MULTIPLE FRACTURES ASSOCIATED WITH SUBDURAL HEMATOMA IN INFANCY

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THE association of multiple long bone fractures with subdural hematoma in six infants was reported by Caffey[1] in a recent publication. Since no additional reports of this syndrome have appeared in the literature, the present authors believe it desirable to report a case simulating those described by Caffey and differing only in that the fractures predominated in the flat rather than the long bones.

CASE REPORT

A 10 wk. old white male infant was referred to this hospital with a presumptive diagnosis of osteogenesis imperfecta. The prenatal history was normal except for a mild elevation of the maternal blood pressure during the last trimester. The infant was born at term to a primagravida mother following a 7 hr. uncomplicated labor. The birth weight was 3.6 kg. The parents were unaware of any difficulties during the infant's neonatal hospital stay.

The 7 day old infant was seen at home by one of the authors for routine examination and advice. The physical examination was normal except for a moderate number of thrush lesions in the mouth. Examination disclosed scratch marks on the face, neck and under the tongue; the latter area contained a moderate sized hematoma. Four days later the infant developed difficulty in nursing, fever and rhinitis. Further examination revealed an airway diminished by moderate inflammation, edema and mucoid discharge from the nose and throat. Twelve days later there was no evidence of these findings. Except for slight pallor and occasional snorting type of respiration the physical examination was normal. Measurements of the weight, length and head circumference ranged between the 50-75 growth percentiles and the chest circumference ranged between the 25-50 growth percentiles.* Development was normal for age.

At 10 wk. of age the infant had difficulty in nursing and developed slight fever. A "grating" sensation over the chest was described by the parents when the baby was held. No history of trauma was obtained. Examination revealed a critically ill baby with ashen color having mild clonic convulsions of the left side of the body. Respirations were irregular, rapid and crowing. Considerable mucus was present in the mouth and bronchial breathing was detected in both upper lung fields. The infant was admitted immediately to the St. Francis Hospital, Evanston, Ill., for study and treatment. Immediate therapy was directed at the control of the convulsions and respiratory distress. Shortly after admission a tense fontanelle was noted. Laboratory study revealed RBC 2.45 million with Hgb. 8 gm./100 cc.; WBC 16.2 thousand with 58% polymorphonuclear leucocytes and a shift to the right. Blood platelets, bleeding and clotting times were normal. The spinal fluid was clear, blood-tinged in all tubes, with normal pressure, dynamics and negative smear and culture for organisms. Blood chemistries were normal. Nose and throat cultures revealed Staph. aureus. Chest roentgenogram demonstrated clear lung fields. However, multiple fractures of the ribs were obvious as was a fracture of the coracoid process of the right scapula.

During this hospital course the infant improved initially on fluid and penicillin therapy. On the sixth hospital day he became fretful and had a mild and brief left-sided clonic convulsion. The head circumference enlarged and the fontanelle became more tense. The skull percussion note was normal. A repeat spinal tap again was negative except that the fluid was slightly xanthochromic. Subsequently the left eye was noted to turn inward and some rigidity of the spine and extremities was evident. The infant was then transferred to the pediatric service of the University of Illinois Hospitals with the diagnosis of probable osteogenesis imperfecta, subarachnoid hemorrhage, and possibly a subdural hematoma.

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* Vickers-Stuart Standards.

Physical examination at this hospital revealed a well nourished irritable infant who did not appear acutely ill. The head was suggestively enlarged in the bi-parietal diameter, and there were prominent veins over the scalp. The sclerae had a bluish tint which was not considered abnormal. The extremities were freely movable. Measurements were as follows: head circumference 41.5 cm.; bi-parietal diameter 12.25 cm.; crown-rump length 39 cm. There was no unusual percussion note to the skull but the anterior fontanelle was almost closed. The pupils were regular and equal and responded normally to light; the fundi were normal. The left eye occasionally deviated nasally. The ears, nose, mouth

FIG. 1. A. RG indicating multiple rib fractures with abundant callus formation and fracture of right coracoid process. B. RG of lower extremities showing healing fractures of shaft of left tibia.

and throat were normal. The neck was supple and slight anterior cervical adenopathy was present. The chest expansion was normal; there was no discoloration of the skin. The costo-chondral junctions appeared sharply angulated and beaded. Resonance and breath sounds were of normal quality. The heart rate, rhythm and sounds were normal and there was no demonstrable cardiac enlargement. The liver was palpable 3 cm. below the right subcostal line; the spleen was barely palpable. The abdominal examination was otherwise negative. The genitalia were normal. There was a small hemangioma over the left lower back. Slight resistance of the upper extremities to passive motion was present and was equal bilaterally. Neurologic examination was negative.

Laboratory examination revealed RBC 3.82 million; WBC 10.8 thousand with 39 neutrophiles, 6 monocytes and 55 lymphocytes. Bleeding, clotting and clot retraction times were normal. A Rumpel-Leede test revealed no petechiae. Vitamin C level was 1.35 mg. per cent of whole blood. Prothrombin time was 33 seconds (control 33.2 seconds). Serum calcium was 9.9 mg.; alkaline phosphatase 5.8 Bodansky units. A spinal tap revealed normal pressure and dynamics with a negative Pandy test, a cell count of 184 noncrenated red cells (tap was initially bloody, subsequently grossly clear). Spinal fluid chemistry showed 56 mg. glucose, 743 mg. chlorides and 0.018 gm. total protein. Cultures were negative. Subdural taps disclosed a large amount of reddish-brown fluid under pressure present on both sides. Roentgenographic examination of the chest demonstrated multiple fractures of the ribs with abundant callus formation involving on the right the 1st, 2nd, 4th, 6th, 7th and 11th ribs with an additional fracture involving the acromium process of the right scapula; on the left the 1st, 4th,

5th (2 fractures), 6th (2 fractures), 7th (3 fractures), 9th (2 fractures), 10th, 11th and 12th ribs. Examination of the long bones revealed a fracture of the left tibia at the middle third. (Figs. 1A and 1B.) The skull RG disclosed some enlargement of the fontanelles with mild separation of the suture lines; there was no skull fracture. Although the degree of callus formation at the rib fracture sites varied considerably, the time at which the individual fractures occurred could not be determined. There was no demonstrable evidence of any local or systemic skeletal disease. Calcium balance studies carried on during the hospital study showed a positive balance of 169 mg. calcium/day.

A diagnosis of multiple fractures and bilateral subdural hematoma was made. A survey for other lesions of mesenchymal origin was made and none was found. The history was reviewed with the parents and no instance of trauma no matter how slight could be elicited. There was no available history of trauma in the immediate neonatal hospital period.

During the subsequent hospital course a repeat subdural tap 10 days later again revealed a similar fluid in both subdural spaces. The neurosurgical department then performed bilateral burr holes and a thin membrane on the right was demonstrated but none on the left. The subdural spaces were irrigated and a drain was inserted on the right which was removed 2 days later. A subdural tap 14 days later revealed fluid in both spaces, more on the right. One month after surgery the infant had 2 successive left-sided clonic convulsions of 5 min. duration. A subdural tap at this time revealed 5 cc. of xanthochromic fluid on the right side. A subsequent ventriculogram showed no evidence of distortion. From this time the hospital stay was completely uneventful.

The most recent examination of the patient at 2 yr. of age and 1 yr. after hospital discharge disclosed a normally developing boy. There have been no additional fractures or convulsions. Complete healing of the previous fractures was observed. The measurements and percentiles were as follows: weight 13.2 kg. (50-75 percentile), length 85 cm. (25-50 percentile), head circumference 51.0 cm. (75-90 percentile), chest circumference 51.5 cm. (50-75 percentile), biparietal diameter 14.5 cm. and occipito-frontal diameter 18.5 cm.*

Comment

The factors responsible for the coincidence of multiple fractures with subdural hematoma in infancy are not clearly evident. Caffey has pointed out that although a traumatic origin might be suspected, no such evidence has been demonstrated in his series. Careful evaluation for any local or systemic skeletal disease added no further information. Similar circumstances exist in this case study.

From Caffey's report and this case study, it should be emphasized that the occurrence of fractures in infancy may be associated with subdural hematoma. Physicians should be aware of this interrelationship. As more cases are recognized the association of these two conditions may become clarified.

Summary

An infant with subdural hematoma associated with multiple fractures was presented. The etiology was not established.

Reference

1. Caffey, J., Multiple fractures in long bones of infants suffering from subdural hematoma, Am. J. Roentgenol. **56**:163, 1946.

Spanish Abstract

Multiples Fracturas Asociadas a un Hematoma Subdural

Se presenta el caso de un niño con un hematoma subdural y fracturas multiples. No se establece etiologia.

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* Vickers-Stuart Standards.

VITAMIN E LEVELS IN TERM AND PREMATURE NEWBORN INFANTS

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ALTHOUGH the normal adult plasma vitamin E level is well established, there has been very little written about this level in the newborn group. This study was done at the Hartford Hospital in conjunction with experimentation on the use of vitamin E in retrolental fibroplasia, a disease almost wholly limited to premature infants. It was felt that if this disease, or any other syndrome, represented a true vitamin E deficiency, a correspondingly low serum tocopherol level might be found. It is not the purpose of this paper to discuss whether a plasma level is truly representative of the amount of available vitamin E in an infant, nor is it to discuss the value of vitamin E in retrolental fibroplasia, but merely to establish the blood tocopherol level in the term and premature infant at birth and immediately after birth.

The average adult level of plasma tocopherol was first determined by Wechsler[1] as .96 mg./100 cc. in 12 patients. Harris[2] found an average level of 1.04 mg./100 cc. in 70 adults. Quaife and Harris[3] reported an average level of 1.20 mg./100 cc. in 13 adults.

In a younger group of nine normal children aged 5 to 15 years, Minot and Frank[4] found an average tocopherol level of .88 mg./100 cc.

In term infants at birth, the average tocopherol level was found to be .34 mg./100 cc. in 54 cord blood tests by Straumfjord and Quaife.[5] Varangot,[6] however, reported an average cord level of .10 mg./100 cc. in 18 infants. Engel[7] recently reported the average level in newborn infants to be .19 mg./100 cc.

The only report on premature infants was by the Owens[8] who found an average level of .25 mg./100 cc. in 46 infants with birth weights of 1.3 kg. or less, these levels being taken between 2 and 8 weeks of age.

In this study the cord blood was obtained by the obstetrician at delivery. The blood was collected in a dry sterile test tube from the placental end of the umbilical cord before or just after delivery of the placenta and is, therefore, a mixture of arterial and venous blood. Blood on the term infants was obtained from the femoral vein and collected in a dry sterile test tube. Blood on the premature infants was obtained by a heel puncture using a blood pipette and put in a tube containing a drop of 10 per cent sodium citrate. All specimens were immediately centrifuged and the serum or plasma sealed in a one cc. ampule. Vitamin E determinations were done under the direction of Dr. V. E. Kinsey at the Harvard Medical School by the micromethod devised by Quaife[9] using only .06 cc of serum. There was no difference in levels between serum or plasma.[10]

Table 1 summarizes the findings in this study. A further breakdown of these figures is presented in the following tables. A total of 191 determinations was done on 53 term infants and 32 premature infants, all of whom had an uncomplicated hospital course. It can be noted from table 1 that there is no significant difference in the tocopherol levels

From the Hartford Hospital, Hartford, Conn.
(Received for publication April 15, 1950.)

of term infants of different weight groups which is in agreement with Straumfjord and Quaife.[5] Although there are too few levels in the smallest weight groups there appears also to be no relationship of the level to the weight in the premature infants.

A comparison of cord blood to day-one blood was done on 33 term infants. This is presented in table 2. Blood was drawn within 2 to 24 hours after birth from the femoral vein of these infants, their cord levels having been taken at delivery. An average value of .22 mg./100 cc. was found for the cord levels while the day-one levels averaged

TABLE 1

TOTAL NUMBER OF VITAMIN E DETERMINATIONS IN MG./100 CC. SERUM ON 85 NORMAL INFANTS IN RELATION TO WEIGHT AND AGE

Birth Wt. (kg.)	Cord		Day 1		Day 2–7		Wk. 1–4		Mo. 1–2		Mo. 2–4		Mo. 4–6	
Term	No.	Av.	No.	Av.	No.	Av.	No.	Av.	No.	Av.	No.	Av.	No.	Av.
3.6 & over	10	.21	10	.21	3	.30								
3.2–3.6	19	.24	17	.22	10	.39								
2.5–3.2	17	.28	13	.24	6	.34								
Premature														
1.8–2.3	3	.25	4	.24	6	.22	8	.24	9	.32	2	.57	1	.45
1.3–1.8	2	.13	4	.13	6	.28	12	.18	11	.27	8	.47	3	.43
0.9–1.3	0	—	1	.37	3	.47	2	.14	1	.38	0	—	0	—

TABLE 2

COMPARISON OF CORD TO DAY 1 VITAMIN E LEVELS IN MG./100 CC. SERUM IN 33 TERM INFANTS

	No. of cases	Average	Median	Range	Standard deviation
Cord	33	.22	.22	.08–.48	.13
Day 1	33	.24	.23	.02–.41	.15

.24 mg./100 cc., which is not significantly different. It is important to keep in mind the high degree of variation among levels as shown by the high standard deviation present throughout this study. Such variation must be expected, however, and is no greater than that found in most reports on this subject. Although the average of cord and day-one levels were equal in these cases, in any given case there was a variation of as much as 50% to 75% in either direction; hence, the cord level can be used only as a rough guide to the level present in the infant during the first day. The difference in values between arterial and venous blood may be of some importance here but no study was done on this subject.

Using either the cord level or the level within the first 24 hours interchangeably, we can establish the tocopherol level at birth by taking either of these values or an average of both if both values were taken. This was done in table 3 to compare the levels at birth of the term infant to the premature infant. An average level of .24 mg./100 cc. was found for the term infants and .22 mg./100 cc. for the premature infants with a median

of .23 mg./100 cc. for both groups. This indicates further that there is no difference between the term and premature infant tocopherol levels at birth.

Table 4 presents a comparison of the levels taken in term and premature infants after the first 24 hours. In 19 term infants the average tocopherol level, taken between the second and fifth days, was .36 mg./100 cc., a figure somewhat higher than that at birth. In the premature infant, as seen in table 1, there appeared to be no significant rise in the tocopherol level until after the second month. In 32 premature infants the levels taken during this time averaged .26 mg./100 cc., not significantly higher than

TABLE 3

COMPARISON OF TERM TO PREMATURE VITAMIN E LEVELS IN MG./100 CC. SERUM AT BIRTH*

	No. of cases	Average	Median	Range	Standard deviation
Term	53	.24	.23	.06–.50	.14
Premature	11	.22	.23	.04–.46	.13

* Cord or Day 1 blood or an average of these if both were taken.

TABLE 4

COMPARISON OF TERM TO PREMATURE VITAMIN E LEVELS IN MG./100 CC. SERUM IMMEDIATELY AFTER BIRTH*

	Age	No. of cases	Average	Median	Range	Standard deviation
Term	2–5 days	19	.36	.38	.09–.56	.15
Premature	2 days–2 mo.	32	.26	.23	.02–.56	.16
Premature	3 mo.–6 mo.	9	.50	.55	.30–.63	.12

* Where more than 1 level was taken on the same patient an average was taken.

that at birth, the median being .23 mg./100 cc., exactly that of the premature infant at birth. This level corresponds well with the .25 mg./100 cc. for this same group reported by the Owens.[8] In nine premature infants whose levels were taken between the third and sixth month of life, an average level of .50 mg./100 cc. was found, significantly higher than those under 2 months of age.

This author's findings were in agreement with those of the Owens in that no relationship was seen between the tocopherol levels in premature infants who had normal eyes and those who developed retrolental fibroplasia. With 150 mg. of vitamin E daily the tocopherol level in the serum of premature infants was found to be between 2 and 5 mg./100 cc. The significance, if any, of the failure of the premature infant to increase his tocopherol level until after 2 months of age while the term infant's level is higher after only five days is not known.

CONCLUSIONS

Evidence has been presented to show that:

1. The average vitamin E level in plasma or serum at birth is .23 mg./100 cc. with wide variations in both term and premature infants regardless of birth weight.

2. The average level of vitamin E in cord blood is equal to the average level of the infant's blood taken within the first 24 hours, although in any one case they may vary as much as 50% to 75%.

3. The vitamin E level in term infants appears to be higher after five days, averaging .36 mg./100 cc.

4. The vitamin E level in premature infants does not increase for two months. Between three and six months of age it increased to an average of .50 mg./100 cc.

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Spanish Abstract

Niveles Sanguineos de Vitamina E en Recién Nacidos a Termino y en Prematuros

Este estudio fue hecho para establecer el nivel sanguineo de vitamina E en el recién nacido y comparar este nivel en aquellos nacidos a termino y prematuramente, en el momento del parto, y poco tiempo después.

Se observó que al nacer el promedio de los niveles sanguineos de vitamina E en 64 niños era de 0.23 miligramos/100 cc con una "standard deviation" de 0.13 miligramos/100 cc tanto en los nacidos a termino como en los prematuros, cualquiera que fuese el peso al nacer. Después de cinco dias en los nacidos a termino el promedio de vitamina E fué de 0.36 milagramos/100 cc mientras que en los prematuros no se observó ningun aumento del nivel sanguineo durante los dos primeros meses de edad. El nivel sanguineo de vitamina E en los prematuros entre tres y seis meses de edad aumento a 0.50 miligramos/100 cc. En 33 recién nacidos a termino el promedio de los niveles sanguineos de vitamina E determinados en la sangre del cordon umbilical fué igual al nivel promedio obtenido en muestras de sangre 24 horas después del nacimiento, pero estas cifras variaron en algunos casos del 50% al 75%.

Hartford Hospital

GASTRIC ULCER OF THE PYLORUS SIMULATING HYPERTROPHIC PYLORIC STENOSIS

Report of a Case in an Infant Nine Weeks Old

By ARTHUR R. C. COLE, M.D.
Toronto

PEPTIC ulcer in infants was first described by Cruveilhier in 1929.[1] In 1941, Bird, Limper and Mayer[2] published a comprehensive review of 245 cases of peptic ulcer in infancy and childhood which they gathered from medical literature up to that time.

Early writers tended to stress the rarity of the condition.[3-5] Most of the more recent articles[2, 6-12] suggest that its apparent rarity is due to the failure of physicians to consider such a diagnosis when dealing with infants and children. This may reasonably be attributed to the influence of earlier textbooks and articles.

The following review of the natural history of the disease represents a condensation of various published descriptions.[2, 3, 12-14]

ANATOMY AND PATHOLOGY

Duodenal ulcers are found three times as often as gastric ulcers. In the newborn infant the ratio is 2:1.[2] Other parts of the gastrointestinal tract are rarely affected. Gastric ulcers are located, in descending order of frequency, near the pyloric ring, on the posterior wall, in the cardia or on the anterior wall. In the duodenum they are situated on the posterior wall above the ampulla of Vater. They may show acute, subacute or chronic inflammatory changes. Extremely acute ulcers may extend to the serosa and perforate before operative interference is feasible. They show no induration of the wall or cellular reaction in the tissues around them. A less acute perforating process may be walled off by bands of adhesions and occasionally extend into the pancreas. Thrombotic vessels may be found in the mucosal, submucosal or muscular coats.

ETIOLOGY AND PATHOGENESIS

This is obscure at all ages. The following conditions have been found in association with peptic ulcer in infancy and childhood with sufficient frequency to suggest a causal relationship:

1. Bacterial infection, especially those accompanied by bacteremia; also suppurative or tuberculous meningitis;
2. Local nonbacterial inflammation such as nonspecific gastritis;
3. Following burns and scalds (Curling's ulcer);
4. Physical injury such as direct epigastric trauma;
5. Circulatory disturbances leading to anoxia of the mucous membrane with devitalization and subsequent digestion by gastric juice, among which may be mentioned asphyxia,

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hyperperistalsis associated with congenital duodenal stenosis, hemorrhagic disease of the newborn infant and disturbance of vasomotor centers as a result of cerebral disease (Cushing);[15]

6. Marasmus with lowered resistance of the gastric mucosa.

Infants and children are relatively free from some of the aggravating factors described in adults, such as alcohol and tobacco, though they may experience anxiety.

Incidence

There are apparently no geographic limitations; cases have been reported from North and South America, Europe, Asia and Australia, and have been described in the white and colored races.

The age and sex incidence are given by Bird, Limper and Mayer.[2] According to these data 37% of the cases occurred in infants under 1 year of age. There is a lower incidence in childhood and a rise in early adolescence. Although a higher incidence is found in the male in each age group, the difference is slight before the age of 6 years. After this age the preponderance of males appears significant.

Symptomatology

"The signs and symptoms which are present may be few or many, but they are so diversified, as to rob them of pathognomonic significance" (Kennedy,[13] p. 643). There are two main groups, a primary group in which the ulcer fills the foreground of the clinical and pathologic picture, and a secondary group in which the patient is already suffering from a serious condition such as gastroenteritis or a generalized infection, and the ulcer is completely overshadowed. Although there is no clearly defined classification of ulcers, in the primary group, the following arbitrary subdivision of symptoms according to age is useful from a clinical viewpoint: (a) neonatal, 0-14 days; (b) infantile, 14 days-1 year; (c) early childhood, 1-9 years; (d) late childhood, 9-15 years. Each group merges gradually with the succeeding group.

Neonatal Group.—The most important symptom is hematemesis or gross melena, particularly the latter. The ulcer is acute with no cellular reaction or bacterial invasion and the patient shows no evidence, either during life or at autopsy, of intracranial injury or localized or generalized sepsis. The lesion either heals rapidly or causes early death by hematemesis or peritonitis following perforation.

Infantile Group.—This is further divided into four distinct subgroups. I. There are no symptoms, the diagnosis being made at autopsy. Deaths have occurred before the passage of blood by mouth or rectum. II. The presenting symptoms are hemorrhage, melena or hematemesis, or evidences of perforation followed by peritonitis. Death is a common sequel. The ulcer is acute in type. III. The presenting symptom is vomiting, which may be projectile and is due to severe pylorospasm. IV. The symptoms are vague. The infant often takes its feeding and gains well for a few weeks or months. This is interrupted by an infection, especially upper respiratory. Following the infection the infant fails to thrive, is unwilling to take or finish feedings. Vomiting, attacks of abdominal pain or discomfort, loose stools, evidence of dehydration or acidosis, occasional streaking of the vomitus or stool with blood, are also seen. Many infants with peptic ulcers have a peculiar puppy-like cry. At times some infants cry as if they had colic. All these symptoms may continue over a period of weeks or months and are considered manifestations of a

gastroenteritis until graver symptoms present with signs of severe hemorrhage or perforation. The previously scaphoid abdomen balloons up following perforation. The infant may suddenly begin to scream, vomit and draw up its legs. This picture of a subacute or chronic ulcer frequently ends in death.

Early Childhood.—In the age group of 1 to 9 years, the symptoms are vague. Often there is anorexia, failure to gain, with upper abdominal pain and sometimes tenderness. The abdominal pain is usually longstanding, recurrent or chronic. Night and prebreakfast pain are generally absent. The abdominal pain is para-umbilical in the younger half of this group and epigastric in the older. Sometimes there is associated anemia. An upper respiratory infection is concomitantly present in some patients. Pyrosis, acid eructations and flatulence are absent. Relief following treatment with alkaline preparations is noted more often in the older half of this group. Nausea and vomiting are uncommon. The ulcers in this group are frequently chronic and may be present for a long time.

Late Childhood.—In the preadolescent years, 9 to 15, peptic ulcer usually assumes its characteristic adult features and may be recognized by the usual diagnostic procedures for adults.

Differential Diagnosis

In patients showing melena, outside sources of blood such as bleeding from the nose or mouth or from the nipple of the mother must be excluded.

In the newborn infant, hemorrhagic disease, syphilis, sepsis per se, congenital blood dyscrasias such as hemophilia, leukemia, thrombocytopenic purpura and congenital fibrinogenopenia must be ruled out.

In infants, the condition may be difficult to distinguish from pylorospasm, hypertrophic pyloric stenosis, gastroenteritis and intestinal obstruction. Other more common causes of gastrointestinal bleeding are intussusception, colitis, polyposis, anal fissure, Meckel's diverticulum, duplication of the intestine, intestinal parasites, neoplasms and Banti's syndrome.

In cases where acute or recurrent appendicitis is suspected, with an atypical picture, peptic ulcer should be included in the differential diagnosis.[16–18] The possibility of peptic ulcer should also be considered in the presence of vague digestive symptoms commonly ascribed to teething, worms, neurosis or allergy.[12,19] As Proctor[20] states, "The most important single factor in the diagnosis is the realization that chronic peptic ulcer occurs in children."

The following diagnostic procedures should be carried out in cases in which peptic ulcer is among the possible diagnoses:

1. Stool and vomitus should be examined for blood.
2. To assist in determining the level in the tract at which bleeding has occurred, passage of a small duodenal tube or thread to various levels of the intestinal tract is suggested. The tube or thread is removed after marking the point opposite the upper alveolar ridge, and the guaiac test for blood is done.
3. A flat plate of the abdomen should be taken to rule out obstruction or perforation. Roentgenograms of the stomach following a barium meal may be made. Assay of gastric acidity following a test meal or histamine injection is unsatisfactory as a diagnostic aid in young infants and children.

Treatment

As in adults, the treatment of uncomplicated cases consists of a dietary regimen with

the addition of alkaline preparations. Where obstruction, perforation, or persistent severe abdominal pain are present, surgical intervention is indicated.

Prognosis

In a partial review of the literature from January 1, 1938 to July 1, 1948, 31 cases of peptic ulcer in infants under 2 years of age were collected, 28 of which terminated fatally.[2, 6, 8–11, 17, 19, 21–27]

In this age group, peptic ulcer is usually unrecognized prior to postmortem examination. Where the condition has been recognized and proper therapy given, infants have recovered in a few instances.

The age at operation or death ranged from 34½ hours to 22 months. Seventeen were male, 14 were female. Twenty-one cases showed duodenal ulcer and 10 cases showed gastric ulcer. Eight patients underwent operation. Of these, three survived. Laparotomy was performed after RGs had shown perforation of a viscus in 2 cases, and obstruction of the duodenum in 1 case. One of the three, an 11 day old female infant, died of other than gastrointestinal disease, 10 days after operation.[21] Autopsy was not performed in this case (Thelander and Mathes). The other two, a 34½ hour old female infant (Bird, Limper and Mayer[2]), and an 11 month old male infant (Schwartz and Halberstam[22]), recovered satisfactorily. The remaining 28 were diagnosed at autopsy or at laparotomy with subsequent autopsy. Many showed signs and symptoms of ulcer prior to death, such as hematemesis, melena or intestinal obstruction following perforation.[2, 6, 8–11, 17, 19, 21–27]

Older children have a more favorable prognosis. Fifty cases occurring in children, between the ages of 2 and 15 years, were collected from the literature of the 10 years ending July 1, 1948.[7, 9, 11, 16–19, 23, 25, 28–40] Thirty-four were male and 16 female. There were 42 cases of duodenal ulcer and 8 cases of gastric ulcer. Forty patients survived with medical and surgical treatment. Thirty-four of the patients showed roentgenographic evidence of ulcer. Melena and abdominal pain were frequent symptoms. Operations were performed in 13 cases, in 4 of which the preoperative diagnosis was appendicitis. An appendectomy was performed and the presence of an ulcer was not appreciated. One patient so treated died later of hemorrhage from a duodenal ulcer. The remaining three were diagnosed by RG following operation and recovered after dietary therapy. In the other 9 cases, various operations were performed, namely gastroenterostomy, closure of perforated ulcer with omentum, pyloroplasty with excision of ulcer, gastroduodenostomy, and gastric resection. All patients survived the operation; two were followed for 12 and 14 years, respectively, with no recurrences.

Of the 10 cases which came to autopsy, 8 had severe coexistent disease. Meningitis was found in 3 cases, fibrocystic disease of the pancreas in 1 case, pneumonia and empyema in 1 case, nephrosis in 1 case, rheumatic carditis in 1 case and right-sided spontaneous pneumothorax in 1 case. In the case of fibrocystic disease of the pancreas, the ulcer was recognized clinically and confirmed by RG prior to death. Of the 2 cases remaining, 1 had an appendectomy and terminated with hemorrhage from a duodenal ulcer 3 days later. The other case showed a duodenal ulcer with hemorrhage with no coexistent disease.

Case History

G. L. E., a 9 wk. old boy of Negro parentage, was admitted to the Babies Hospital with the complaint of vomiting after every feeding since the 5th or 6th day of life. Family history irrelevant.

The infant was the result of a normal full term spontaneous delivery. Birth weight was 2730 gm. From the 5th or 6th day of life the infant vomited most of every feeding shortly after finishing it. The feeding given was made up of 4 oz. evaporated milk, 8 oz. of water and 1½ tsp. of sugar. Orange juice was offered and refused. Oleum percomorphum was given during the first week and discontinued as the mother felt it was choking the baby. When the infant vomited she would refeed him sometimes and felt that more of the second feeding was retained. No projectile vomiting was ever noted. There was regurgitation through the nose. The vomitus was always white and curdy, never brown or bile-stained. When not vomiting, the infant always appeared alert, active and ravenously hungry, sucking at his fists. Constipation was noted from birth. Milk of magnesia, 4 to 5 drops per bottle, was given every 2 to 3 days. This occasionally produced a moderately soft stool. Usually the stools were hard and small, 1 or 2 per day. The infant screamed with almost every bowel movement. The day prior to admission a single very dark, almost black, stool was passed.

The infant had 2 convulsions, 2 wk. and 1 wk. before admission. During these, the arms and legs were stiffened and straight, the eyes rolled up and the face became cyanotic. Each lasted 4 to 5 min. and occurred during vomiting episodes.

Physical Examination

On admission, examination revealed an irritable, hungry, poorly nourished, moderately dehydrated Negro infant. His weight was 2620 gm. The temperature was 36.2° C., pulse rate 130/min. and respiration 26/min. The anterior fontanelle was depressed. The respirations were shallow and irregular; every third or fourth breath was gasping in nature. The heart and lungs were considered normal. There was a palpable pyloric tumor. Peristaltic waves were seen. The skin turgor was fair. A diagnosis of pyloric stenosis was made.

Laboratory Examination

The initial blood count showed RBC 4.8 million/cmm. and WBC 7 thousand/cmm. with 50% polymorphonuclear leukocytes, 36% lymphocytes and 4% monocytes. Hemoglobin content was 12.0 gm./100 cc. There was no sickling. A complete urinalysis was noncontributory.

Course

The infant was hydrated with intravenous fluids; 250 cc. of 5% dextrose in saline and 70 cc. of 5% dextrose in distilled water, were given. He took and retained 90 cc. of formula. Two days after admission, through a high right rectus incision, a Fredet-Rammstedt operation was performed. Both prior to and at operation, the surgeon felt that the pyloric tumor was not typical.

The day following operation, at 3:00 a.m., Cheyne-Stokes breathing developed. The heart beat became irregular. Foreign material resembling vomitus and mucus was seen in the nares. The extremities became cold and the nailbeds cyanotic. Rales were heard in the left anterior chest. It was felt that the infant had aspirated some vomitus. Continuous oxygen, and suction as necessary, were administered. Caffeine sodium benzoate 0.02 gm. was given by injection. The infant vomited some brownish material. A transfusion of whole blood 55 cc. was given. At 4:45 a.m. caffeine sodium benzoate was given again in the same dosage. The heart seemed more regular and the color improved. The temperature at that time was 35° C. External heat was applied (in the form of hot water bottles). At 7:30 a.m. the respirations were still gasping. The cardiac activity was regular. The pulse rate was 100/min. The abdomen was soft and there were no fluid waves nor dullness. Shortly following this examination, the infant began to exude a serosanguineous discharge from the nose and mouth. He died at 8:10 a.m.

Clinical Diagnosis

1. Hypertrophic pyloric stenosis.
2. Fredet-Rammstedt operation—pyloromyotomy.

Postmortem Macroscopic Observations

The necropsy was performed 5 hr. after death. The body was that of a dystrophic and dehydrated Negro male infant. Two centimeters from the midline a right rectus incision extended downwards from the costal margin, 4.5 cm.

On opening the peritoneal cavity, hemorrhage was seen in the anterior abdominal wall adjacent to the incision. Fluid escaping from the incision appeared sanguino-purulent. A small amount of bloody fluid was present in the paracolic gutters. A large black soft clot was present in the splenic ligament.

The carotid arteries were noted to arise by a common trunk from the aorta 2.4 cm. above the aortic valve. The left subclavian artery arose from the arch just distal to this vessel. Slightly posterior to the left subclavian artery the origin of the right subclavian artery was seen. The latter vessel ran behind the esophagus and trachea toward the right arm. The right lung sank in water. The left lung floated.

The mucosa of the lower portion of the esophagus showed a red coloration and a finely granular appearance. The muscle coats appeared hypertrophied.

The stomach was diffusely thick-walled with hypertrophy of the muscularis, and the mucosa was bright pink and showed a large amount of mucus. The lumen contained milk, food and mucus with changed blood in it. On the midanterior surface of the pylorus there was a recent longitudinal incision 1.3 cm. in length (Fig. 1a) which gaped slightly and showed hemorrhage in it. No hypertrophy of the pyloric musculature was evident. There was a prepyloric rounded elevation in the

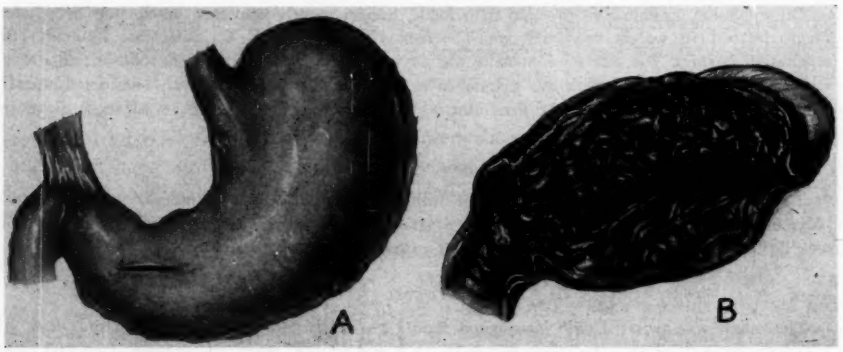

FIG. 1. A. Anterior aspect of stomach showing thickened pylorus and pyloromyotomy. B. Mucosal surface of pylorus showing ulcer with thickened mucosa forming margin.

lesser curvature which extended a distance of 1 cm. from the surface and had a diameter of 2 cm. at the base. Beneath the incision, on the mucosal surface of the stomach, a large gastric ulcer was seen (Fig. 1b). It measured 2.0 x 1.7 cm. and was 4 mm. in depth. It extended distally to within 3 mm. of the duodenum, on the anterior and superior mucosal surface of the pylorus. It extended very slightly below the Rammstedt incision. The ulcer base was smooth, triangular in shape, and appeared to extend to the muscular coat. No perforation or hemorrhage was noted in the base. The mucosa was heaped up around the ulcer. Proximally there was a rounded mass of mucosa 0.9 x 0.9 x 0.5 cm. Section through this mass revealed the thickening to be superficial; it was due in part to thickened submucosa and in part to hyperplasia of the mucosa which at the margin of the ulcer measured 2 mm. in thickness in the microscopic section. Proximal to this again the mucosa was thin and bulged outward, away from the lumen. The bulging corresponded with the deformity described above in the lesser curvature.

The mesentery of the bowel from the second portion of the duodenum to the sigmoid colon was long and free. The mesenteric attachment of the bowel lay along a line extending from the third portion of the duodenum to the inferior pole of the right kidney.

A complete autopsy was done. The other organs showed no unusual gross findings.

MICROSCOPIC EXAMINATION

Lung: The alveoli were flooded with edema fluid, red cells and some lymphocytes. Many phago-

cytes, some with ingested debris, were noted. Diffuse and partial atelectasis was observed in some areas.

Stomach: Section through the prominent mass of mucosa proximal to the ulcer confirmed the impression that the increased thickness was chiefly due to mucosal hyperplasia. No chief cells were seen in the mucosa. The muscle coats did not appear hypertrophied. The submucosa was thickened with fibrous tissue and showed small and large collections of lymphocytes.

Pyloric Ulcer: The marginal mucosa was ragged and overhanging. No mucosa was seen in the ulcer base. The edges were undermined. The submucosa near the ulcer was thickened and showed increased numbers of blood vessels. The ulcer base consisted of fibrous tissue of varying density in which were scattered lymphocytes. A blood vessel was seen near the ulcer surface. There were scattered lymphocytes in the external circular muscle coat and subperitoneal layers.

Pancreas: The peripancreatic and interlobular fibrous tissue was not increased in amount but showed edema. A hemorrhage was present on one surface. In a circumscribed area near the hemorrhage, there was a collection of lymphocytes, polymorphs, phagocytes and fibroblasts.

Adrenal: There was edema of the periadrenal connective tissue.

Microscopic examination of sections of the other organs was noncontributory.

TABLE 1

CASES OF PEPTIC ULCER FOUND AT POST MORTEM, BABIES HOSPITAL
January 1, 1924–January 1, 1950

	Gastric Ulcer	Duodenal Ulcer	Gastric and Duodenal Ulcer
No. of Cases (total 31)	9	21	1
Sex—Male	5	11	1
Female	4	10	
Age— 0–14 days	3	0	
15 days–1 yr.	2	13	
1 yr.–9 yr.	2	7	1
9 yr.–15 yr.	2	1	

ANATOMIC DIAGNOSES

The following diagnoses were made: Gastric ulcer with hemorrhage, hyperplasia of gastric mucosa around the ulcer with partial obstruction. Operation: Fredet-Rammstedt pyloromyotomy. Aspiration of blood, edema of lungs, hemorrhage at operative site, common trunk origin of right and left carotid arteries from aorta, anomalous origin and course of the right subclavian artery, incomplete rotation of large bowel with free mesentery of colon.

DISCUSSION

In retrospect the indications that the condition was not pyloric stenosis were the age of the infant, lack of projectile vomiting, the dark, almost black, stool passed the day prior to admission and the atypical nature of the tumor noted by the surgeons. Without the assistance of examination of the stool or vomitus for blood or RGs of the stomach following a barium meal, the correct diagnosis could not have been established. From the size of the ulcer at necropsy it is probable that roentgenographic studies would have identified the lesion.

Finny[41] described the case of an infant with ulcer below the pyloric ring, causing

pylorospasm, persistent forcible vomiting, and marked peristaltic waves. In the infant group, pyloromyotomy has been performed in two cases of duodenal ulcer. One, aged 2 months (Bode[42]), died; the other, aged 6 months (Palmer[43]), recovered. Meiselas and Russakoff[10] suggested that all infants who have projectile or persistent vomiting should be investigated roentgenographically.

No case similar to the one presented has previously been reported, to the writer's knowledge, where the clinical findings, including a palpable tumor, were so indicative of pyloric stenosis and the main pathologic finding was gastric ulcer of the pylorus.

Table 1 summarized the 31 cases in which peptic ulcer was found at autopsy at the Babies Hospital from January 1, 1924 to January 1, 1950. During this time 2,468 autopsies were performed; the incidence of peptic ulcer is 1.25%.

TABLE 2

DISEASE COEXISTENT WITH GASTRIC AND DUODENAL ULCER

System and No. of Cases	Coexistent Disease	Babies Hospital		Literature	Reference No.
		Gastric Ulcer	Duodenal Ulcer	Peptic Ulcer	
Central nervous 13 Cases	Suppurative and tuberculous meningitis	1	4	2	32, 44
	Intracranial injury	1		2	30, 46
	Status marmoratus (1 case, ulcer at both sites)	1	1		
	Intracranial tumor			1	45
	Localized hydrocephalus			1	48
Gastrointestinal 6 Cases	Infection of gastrointestinal tract	2	2	1	50
	Torsion of stomach and diaphragmatic anomaly			1	49
Respiratory 5 Cases	Acute laryngeo-tracheo-bronchitis		1		
	Congenital laryngeal stridor		1	1	17
	Pneumonia		2		
Diseases of blood 4 Cases	Agranulocytosis, clinical	1			
	Erythroblastosis	1	1	1	47
Disease of pancreas 3 Cases	Pancreatic fibrosis with bronchiectasis		2	1	36
Genitourinary tract 3 Cases	Chronic glomerulo-nephritis		1		
	Anomalies of G.U. tract with infection		2		
Heart disease 3 Cases	Rheumatic heart disease	1		1	9
	Congenital heart disease		1		
Liver disease 2 Cases	Atresia of bile ducts		1		
	Cirrhosis of liver			1	51
Tumors 2 Cases	Lymphosarcoma	1			
	Wilms' tumor		1		
Generalized infection 2 Cases	Miliary tuberculosis		1		
	Syphilis			1	53
Other 3 Cases	Marasmus		1		
	Burns			1	52
	Trauma to abdomen			1	34
Total 46		9	22	16	

The sex ratio in this series is almost 1:1 as compared to 3:1 found by Bird, Limper and Mayer.[2] Eighteen cases were in infants under 1 year. Thirteen are between the ages of 1 and 15 years. The oldest patient in the series was 11 years, 11 months, and the youngest was 3 days of age. This is in contrast to the series of Bird, Limper and Mayer,[2] who list 89 cases below the age of 1 year and 154 between the ages of 1 and 15 years. A factor accounting for some of the discrepancy is that clinical cases at Babies Hospital which have been diagnosed and treated successfully are not recorded in this series. Some of them have been previously reported.[11] In only one of the cases which came to autopsy was the diagnosis of peptic ulcer suggested during life. The diagnosis was based on the clinician's previous experience in a case with gross melena which showed peptic ulcer.

In the author's series of cases with gastric ulcer or ulcers, a coexistent disease was noted in all except the present case. With the exception of three cases, the lesions were small and measured less than 3 mm. in diameter. In eight cases there were multiple lesions.

In the series of cases of duodenal ulcer coexistent disease is noted in all cases. In three cases only could the ulcer be considered as the primary cause of death or antecedent to the conditions causing death.

In the one case showing ulcers of both stomach and duodenum, a primary diagnosis of status marmoratus was made.

Table 2 summarized the coexistent and primary causes of death found in the author's cases of peptic ulcer and also in those collected from a partial review of the literature from January 1938 to July 1948.[9, 17, 30, 32, 34, 36, 44–53]

It is apparent from the findings in these cases and in the literature that peptic ulcer occurs frequently in association with disease of the central nervous system, especially meningitis, and with diseases of the gastrointestinal tract and respiratory infections.

Summary and Conclusions

A brief review of the natural history of peptic ulcer in infancy and childhood is given. The symptomatology, differential diagnosis and diagnostic procedures are presented. The diagnosis of peptic ulcer should be considered more often in infancy and childhood and the proper diagnostic procedures instituted.

A case of gastric ulcer simulating hypertrophic pyloric stenosis is presented. A summary of 31 cases with peptic ulcers found at autopsy at the Babies Hospital from January 1, 1924 to January 1, 1950 is given.

From a summary of coexistent disease found in the autopsy cases at the Babies Hospital and reports from the recent literature, it would appear that diseases of the central nervous, gastrointestinal and respiratory systems are commonly present in cases which have shown peptic ulcer at autopsy.

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SPANISH ABSTRACT

Ulcera Gastrica del Piloro Simulando una Estenosis Hipertrofica Pilorica; Reporte de un Caso en un Niño de Nueve Semanas de Edad

Se presenta una revisión de la historia natural de las ulceras pepticas en la infancia y niñez. La sintomatologia, diagnostico diferencial y procederes diagnosticos son presentados. El diagnostico de la ulcera peptica debe ser considerado mas frecuentemente en la infancia y niñez, y los exámenes de diagnostico apropriados deben ser realizado.

Se presenta un caso de ulcera gastrica simulando el cuadro clinico de una estenosis pilorica. El autor hace un sumario de 31 casos con ulcera peptica encontrados en autopsias realizadas en el Babies Hospital durante el periodo de 1/1/1924-1/1/1950. Del sumario de las enfermedades co-existentes encontradas en la autopsias de estos casos en el Babies Hospital asi como del estudio de otros reportes recientes, se destaca el hecho que enfermedades del sistema nervioso central y respiratorio son encontradas frecuentemente asociadas a las ulceras pepticas.

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Round Table Discussion

ENDOCRINE THERAPY IN CHILDHOOD

WILLIAM A. REILLY, M.D., Little Rock, Ark., *Chairman;* LAWSON H. WILKINS, M.D., Baltimore; WILLIAM C. DEAMER, M.D., San Francisco

WILLIAM G. MOTEL, M.D., Chicago, and HARRY F. DIETRICH, Beverly Hills, Calif., *Secretaries*

THYROID EXTRACT—INDICATIONS AND DOSAGE

Chairman Reilly: The first topic that I want to discuss with you is thyroid extract, its indications and usage. This sounds like a hackneyed subject but still there is a great deal of misusage and misinformation about thyroid.

The first thing about thyroid that might be of use to you is its preventive usage. In pregnancy it is probably advisable in the endemic areas where goiter and iodine deficiency occur to give some iodine. I am going to be very dogmatic and didactic and hope that our fellow participants will disagree, if they care to. A good many physicians feel, and I agree, that the pregnant woman should be given a little thyroid substance if it is properly indicated.

Now for the therapeutic use of thyroid. First, the indications are as follows: It is unnecessary to state to you gentlemen that you do not have to use thyroid extract for thyrotoxicosis. I have seen that happen very recently in a child with a great thyroid overactivity and carditis; some one administered a tremendous amount of thyroid inducing further decompensation of the heart. The prime indication for thyroid therapy is real hypothyroidism. Other conditions that still might be indications for thyroid are nephrosis, eczema, ichthyosis, obesity and perhaps prematurity. I am going to be very dogmatic about mongolism. Thyroid extract in mongolism has no use unless the mongol has hypothyroidism. I want to decry the use of thyroid in mongolism, although I have no better therapy. However, I do give it a trial, if for no other reason than to demonstrate to the parents that thyroid will not benefit their child. Now, as to the choice of the thyroid substance. You may have noticed that I said "thyroid substance," not thyroid extract. The latter is a misnomer in my mind. We do not know what thyroid hormone is as yet. It may be 1 or more hormones or substances. Thyroid substance is the proper name, I think, to give to the material we call thyroid extract.

Next we will consider the types of thyroid substances that are available. Thyroxin is available and

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is occasionally used but it is not entirely reliable, often must be given by injection and is not readily procurable. Whether it is preferable to the ordinary dessicated thyroid substance is questionable.

Let us next consider dosage. One grain of a dessicated substance of thyroid is equal to 5 grains of fresh substance (by the U. S. Pharmacopoeia); keep that in mind because the British pharmocopeial product is still marked in this country and is only about ⅓ to ¼ as strong as the American preparations. Let us be circumspect about starting and maintenance doses. You cannot set a dosage of thyroid—it depends much, like insulin, on the individual need of it. You will have to try it out; one cannot state so much per pound because it will not work out that way. I will give you some sample daily maintenance dosages, as follows: A patient 2 to 4 months of age—about 6 mg.; from 4 to 8 months—about 12 mg.; 8 to 12 months of age—18 mg.; 12 to 24 months—25 to 50 mg.; 2 to 4 years—30 to 100 mg.; 4 to 12 years—60 to 200 mg. Two hundred to 250 mg. daily, in my experience, is about the maximum effective maintenance dose with the majority of these patients who need it. You can give this thyroid in 1 dose a day because it is accumulative—it is stored in the body. I like to have the bottle on the table at breakfast and let the child get it right then. I have been very partial to giving calcium and phosphorus to patients taking thyroid over a period of years because of the known leaching effect of thyroid on the skeleton storage of calcium and phosphorus. For the same reason, I give a dosage of vitamin D to help the utilization of calcium and phosphorus. In iodine poor areas, the giving of iodine along with thyroid substance may be helpful; usually, however, the gland does not build more hormone from this extra iodine. However, we have shown that this extra iodine is stored and used elsewhere. When you give these doses of thyroid you do not start the maintenance dose per day. Start circumspectly, as I mentioned, with about 15 mg. once or twice daily. If no untoward symptoms develop during the next 2 weeks, raise the amount. It may be doubled then and the same procedure may be repeated 2 weeks later if this is desirable, depending on the reaction of the patient, results obtained, response of the basal metabolic rate and other laboratory criteria if desired. Effects can be noted in 3 to 5 days after starting an effective dosage. These effects are diuresis, weight loss, increased pulse rate, temperature, basal rate and excessive physical and mental activity. Later on there will be noticed growth increase. I do not know how soon you might expect the blood cholesterol to lower itself; perhaps a few weeks after you start an effective dose. If great mental retardation has existed for a long time, there will be no help but possibly no increase in this mental retardation. The greater the physical deficiency, the less the dose for the maximum improvement.

The basal metabolic rate is not reliable or to be relied upon for regulating the dosage. Clinical evidence of improvement or toxicity, to be described later, is far better as a guide for the proper dosage, in my mind. You hardly need laboratory tests to decide this in office practice. They are very nice to have and they give you mental stimulation and satisfaction in your practicing, but you can get along without them by using clinical criteria. It is undesirable to start in outright myxedema this eventually necessary maximum maintenance dose as the resultant metabolic upheaval is very upsetting to the patient. The more deficient the patient, the less is the maximal effective dose necessary. With too great a dose the patient and the family occasionally stop therapy even with the milder toxicity, that is restlessness, insomnia. They sometimes stop for years, thereby losing irretrievable and valuable time and helpful therapy. Occasionally patients are sensitive to doses of thyroid too small to be effective maximally. This is true of some of the nervous cretins, although usually most of them when treated are less nervous. Now, the following findings should raise the suspicion of overdosage: nervousness, excitability, irritability, insomnia, excessive perspiration and feeling of heat, palpitation, rapid heart action, diarrhea, undue weight loss, toxic appearance of patient with staring eyes (that is not common, however) and elevated basal rate. The appearance of any one or more of these findings justifies diminishing or discontinuing the dose for a few days or a week and usually the disagreeable symptoms promptly disappear. You can then resume at a lower dosage. The drug accumulates as mentioned earlier. Often we allow a patient to stop the medication for a week every month or 2 to prevent this, thereby assuring lifelong therapy. Patients starting therapy should be seen every week or 2 to reach properly the maximal effective dose and then checked periodically for proper maintenance of this dose. It may be well to give a stop notice if the patient does not report for check-ups. Therapy should be stopped with infections. The dosages should be diminished perhaps by half during fever, the seasons of great heat or when patients stay in an altitude of over 3000 feet or subjected to great physical or emotional strain. I do not know of any childhood disease except perhaps pronounced cardiac insufficiency which absolutely contraindicates thyroid therapy.

The great majority require the drug all their lives. Temporary hypothyroidism is occasionally encountered; usually it is mild; medication is needed until the gland resumes its normal function. Rarely is a patient so sensitive to the animal protein of thyroid substance that one must change from one species of animal to another. At present it is rare to find thyroid on the druggists' shelves inert from age, heat or light. The British preparation is only ⅓ the strength of the U.S.P. preparation.

Therapy for the Undescended Testis

The next topic which I will discuss is therapy of the undescended testis. I do not think the profession quite realizes the therapeutic changes which have gone on. If any therapy, other than natura., is indicated surgery has given better results than have hormones by themselves.

The majority, as high as 97%, of elevated testes descend naturally sometime before or at about puberty. Spermatogenesis is not impaired unless the testis is still undescended after puberty. Malignancy is no more frequent than in a descended testis. Only about 3% of adults have undescended testes, and often this is due to anatomic defects—short vasdeferens, adhesions, etc.; surgery is required for these and hormone is given as a supplement.

The patient should be properly quizzed and examined. Has the testis ever been in the scrotum, for instance, when in a hot bath? Examine him in the upright as well as in the recumbent position. The examiner should be gentle, his examining hands should be warm. Inspect carefully. Place a finger on each interval inguinal ring to keep the testis from sliding up the canal into the abdomen. Repeat the examination, if doubtful, some days or weeks later; in the meantime, the parents can watch for the missing testis.

If the testis is found in the canal, its range of mobility should be tested. If it can be placed at least in the upper part of the scrotum, nature will cause its descent in due time, and maybe not until just before puberty when pituitary gonadotrophin is elaborated.

The presence of associated defects occurs in a minority of cases of undescended testis and justifies operative therapy. Particularly these are hernia, ectopic testis, adhesions markedly limiting excursion, hydrocele, abdominal cryptorchidism. Some of these defects should be operated early in the first 2 years of life; i.e., marked hernia, hydrocele; the others should be operated between the third and fifth and probably no later than the eighth year. Hormone, pre- and postoperatively, is urged for it often induces extra growth of the cord and vessels, lessening the technical problem; but hormone by itself will not bring down such testes.

This might be summarized as follows: if associated anatomic defects are to be permanent, surgery is indicated; surgery is necessary in this minority. The majority of undescended testes are mobile, the patient's pituitary gonadotrophin will cause these to descend when it is elaborated sufficiently which is just before or during puberty and this lateness is without risk to function. In this group (majority) hormone can be tried but will not do any more than nature would do ultimately; if descent by hormone or nature does not occur, surgery should be done just before and certainly no later than the age of puberty because spermatogenesis will not develop very often, thereafter. Hormone is given pre- and postoperatively.

The most practical hormones available at present are gonadotrophic, which is stimulative, and male sex hormone, which is substitutive. Theoretically a stimulative hormone is better than a substitutive one but in practice a substitutive male hormone works well and can be given orally.

A good pituitary gonadotrophic hormone would be the ideal one but none such is available for practice, not even for experimental use. So we use the next most ideal, chorionic gonadotrophin. This, particularly from human pregnancy urine, is stimulative mainly for the Leydig interstitial cells and little, if any, for spermatogenesis in the tubules. The chorionic gonadotrophin from pregnant mare's serum is less stimulative for human Leydig's cells. We feel that since most cases lack enough pituitary action that the above gonadotrophins should be given first; most of the time we use the one from human pregnancy urine for reasons stated. At what age should hormone be started? Good authority now states that it can wait until puberty age—11 or 12 years. Personally, I like to start around 8 or 10 years. Do not forget that normally the pituitary gonadotrope doesn't put clinical effects out much before 10 or 11 years. It is not necessary to start hormone therapy at 3 to 5 years for damage will probably not occur in an undescended testicle until after puberty.

Dosage of chorionic gonadotrophin is about 500 international units 3 times weekly subcutaneously or intramuscularly up to a total of about 5000 units for the younger child and 10,000 units for the older boy. If results are not good, after a rest period of about 6 weeks, one can repeat this

again. Testosterone can also be given, if desired, during this second course; the scrota and vasa may develop better. Carefully re-examine the location, mobility, etc., of the testicle 3 to 6 months after the second course to note if there has been failure or success. Now, if successful, do not forget that the hidden physician, Mother Nature, may have been working too, especially around 12 or 14 years, particularly with the boy who otherwise was showing a few sprouts of puberty when you started this therapy.

Male sex hormone, testosterone, is now rarely used by injection. It is more often taken orally as methyl testosterone in a form for absorption through the sublingual mucosa or in a form for absorption in the alimentary canal. For younger children the daily dose is for the average about 10 mg. and for older children from 10 to 20 mg. daily. The dose for perlingual absorption is about ½ to ⅔ the dose for bowel absorption and the absorption of the former is about 2 or 3 times more efficient. It is exceptional now to use injections of testosterone proprionate. The dose would be 5 to 10 mg. for the younger and 10 to 20 mg. for the older child, given intramuscularly 2 to 3 times weekly. Testosterone is continued in the dose to prevent as little, or no, development of other secondary sex characteristics as possible, while trying to bring about the descent of the testicle. The course usually goes on for about 2 months; after a rest period of 6 weeks, a second course can be given as indicated by no or very little progress. In my experience, about 20 to 60% of cases so treated (these are a minority of the whole group) will have descent that one can ascribe to hormone therapy. If it is not curative, it is helpful to the surgeon. It is superfluous to state that if such endocrine therapy then does not produce descent, surgery certainly should be tried very soon thereafter. Descent, after hormone therapy, has been reported in 20 to 60% of cases with re-ascent expected more often giving only male hormone.

Treatment of Delayed Adolescence and of Sexual Infantilism

Dr. Lawson Wilkins: A large proportion of patients brought to an endocrine clinic consists of children who show delay in the onset of adolescence. This condition seems to attract more attention and anxiety from the parents of boys than of girls. By the age of 13 or 14 years most boys show definite signs of sexual development accompanied by an adolescent spurt of growth and increased muscle bulk. However, others fail to show any signs of sexual development and continue to grow at the relatively slow preadolescent rate. Accordingly, they lag far behind their contemporaries in height, muscular development and psychic maturation and are considered "little runts." Not infrequently puberty is delayed until the patient is 15 or 16 years old, and at times it occurs as late as 18 or 19 years. Once begun, adolescence may progress rapidly, accompanied by a rapid spurt of growth; or there may be gradual sexual maturation with comparatively slow growth which may continue for a long time. Many patients who have been small until their late teens eventually attain full adult height; others are constitutionally small individuals.

The studies of Schonfeld, Shuttleworth, Greulich and others have emphasized the wide range in the time of onset and the patterns of adolescence, which in entirely normal individuals may begin anywhere between the ages of 9 and 17 years, and occasionally even outside of this range. These differences are due to constitutional factors, which are sometimes but not always hereditary. That there is only a delay in the activities of the pituitary-adrenal-gonadal mechanism responsible for the initiation of puberty and not a specific defect of some gland is shown by the fact that the patients eventually mature and grow quite normally without any treatment.

When one is confronted with a patient with a prolonged delay of adolescence, it may be difficult to exclude the possibility that the condition might be due to a true and permanent pituitary defect, which actually is quite rare. When the patient is somewhat stunted in growth and retarded in osseous development, many physicians make a diagnosis of pituitary dwarfism without adequate evidence. If considerable obesity is a part of the clinical picture, the diagnosis of Froehlich's syndrome frequently is made incorrectly, in spite of the facts that there are no hypothalamic symptoms and that the obesity is readily explainable on dietary and constitutional grounds. However, in most of the children brought to us at 14 or 15 years, or older, there are already beginning enlargement of the testes, a little pubic fuzz or some other early sign of puberty to suggest that the normal pituitary gonadal mechanisms are beginning to function.

The problems of whether to treat these patients and the time and type of treatment are difficult ones which should not be answered dogmatically. Unfortunately, the parents have usually been told by some well-meaning but uninformed doctor, nurse or school teacher that the child has a "serious

glandular disorder" for which treatment is necessary and urgent. It is true that in boys of this age the injection of chorionic gonadotropin or the oral administration of methyl testosterone will accelerate sexual development and adolescent growth. However, if left alone for 6 months or a year or 2, this growth and development will occur spontaneously. A great many patients are being treated unnecessarily at the cost of considerable expense and discomfort. When such treatment is given, there is a serious possibility that the boy and his parents may be all the more convinced that he really was not normal until given "needles" or pills, and he may carry into later life subconscious feelings of incompetency or inadequacy.

In most instances all that is necessary is for the physician to reassure the boy and his parents that there is no glandular deficiency, that late onset of puberty is by no means uncommon and that within another year or two without treatment he not only will begin to mature but also will grow more rapidly. On the other hand, there are some instances when the small stature, lack of maturity and the over-anxiety of the parents have created such serious feelings of inferiority and insecurity that treatment is desirable. This is particularly true in boys of 16 or 17 years who are attending boarding school and whose small size and underdevelopment excludes them from athletic and social activities and subjects them to teasing or ridicule.

In boys the administration of chorionic gonadotropin, made from the urine of pregnant women and sometimes called "anterior pituitary-like hormone" (A.P.L.), is probably the most rational treatment. This should accelerate the maturation of the patient's testes and stimulate the secretion of androgen by the Leydig cells. Doses of 500 to 2000 R.U. injected intramuscularly 3 times a week are advisable. Occasionally a patient is sensitive to preparations of chorionic gonadotropin and has reactions necessitating its discontinuance. Increased size of the testes and beginning secondary sexual development should be apparent within 2 to 3 months but growth in stature and sexual development may not be rapid and spectacular with this treatment. In some cases where there are urgent reasons for obtaining more rapid results it is justifiable to supplement gonadotropic therapy with androgen in the form of methyl testosterone by mouth. It is probably best to give relatively small doses of 10 to 20 mg. daily. It should be remembered, however, that treatment with either gonadotropin or androgens consists of substituting hormones just as a transitional period of life when the patient's own pituitary-gonadal mechanism should be beginning to function. Furthermore, placental gonadotropin is not identical with either the luteinizing or follicle-stimulating hormone of the pituitary, although its action resembles that of the former. We know of no harm from this treatment or inhibition of pituitary activity when it is given judiciously and over limited periods of time, not exceeding 6 to 12 months. In our clinic attempts are being made to obtain more data concerning the actual effects on the testes by biopsies taken before and after treatment.

In girls retardation of development usually does not cause urgent psychologic problems. Physiologic therapy would consist in treatment with alternating courses of follicle-stimulating and luteinizing hormones. Unfortunately, entirely satisfactory preparations of follicle-stimulating hormone are not available. Hamblen and others have recommended pregnant mare's serum injected over a period of 2 weeks followed by chorionic gonadotropin for 2 weeks. In our hands this has not been very satisfactory as there is frequently sensitivity to pregnant mare's serum. It is probably best not to treat girls unless there is proof of true pituitary or ovarian defect and then to use substitution therapy with estrogen.

As stated previously, it is often difficult before the age of 17 years to decide whether a patient has merely delay in the onset of adolescence or a true pituitary or gonadal defect. In the latter conditions treatment is definitely indicated. The differentiation between pituitary insufficiency and a gonadal defect can be made on the basis of the assay of urinary gonadotropins, which are high in the latter. In girls the possibility of the syndrome of ovarian agenesis, which is not uncommon, should be considered. In males with pituitary insufficiency causing hypogonadism either with or without dwarfism, the effects of chorionic gonadotropin may be tried for a few months. However, the treatment is expensive and inconvenient if it has to be continued indefinitely; and substitution therapy with methyl testosterone in daily doses of 30 mg. is usually resorted to. This brings about rapid development of secondary sexual characteristics and an adolescent spurt of growth and muscular development. There is a rapid increase in weight due to increased muscle bulk rather than fat. The appetite is improved. The growth may amount to 3 to 5 inches in the first year with a total increment of 5 to 9 inches over the next 2 to 3 years, after which it usually ceases due to epiphysial fusion. It is questionable whether the total height attained is greater than would have been reached

eventually in the course of years without treatment. In some cases the testes remain small and atrophic, in others there is considerable growth. In most of our cases testicular biopsies after treatment have shown absence of gametogenic activity but in several there were slight degrees of spermatogenesis. The psychologic improvement with increased self-assurance, energy and ambition is the most important and gratifying result of treatment.

The treatment of the syndrome of ovarian agenesis with cyclic courses of estrogen or of estrogen and progestin orally has been discussed. In females with panhypopituitarism there is deficiency of adrenal androgen as well as the female sex hormones and the patients are lacking in sexual hair as well as breast and vaginal development. In addition to cyclic therapy with estrogen and progestin these patients should be given methyl testosterone in doses of 10 to 20 mg. daily. This brings about growth of sexual hair and increases protein anabolism and growth. When these small doses are combined with the female hormones, virilization does not occur.

Recent Studies on the Effects of Cortisone and ACTH in the Treatment of Various Diseases

The discovery by Hench and his coworkers at the Mayo Clinic that cortisone (compound E of the adrenal) has a remarkable influence on rheumatoid arthritis has aroused great interest and caused hope that hormonal therapy might be of value in this and other types of disease. It was reported that the daily injection of 100 mg. of compound E caused the disappearance of joint and other manifestations of rheumatoid arthritis within a comparatively few days after beginning treatment, but that the symptoms recurred rather promptly after discontinuing therapy. Doses less than 100 mg. daily were generally ineffective. In 1 patient treated over a considerable period, early signs of Cushing's syndrome developed. The same workers later reported that in acute rheumatic fever compound E caused not only a prompt fall of fever and clearing of joint manifestations but a decline of the sedimentation rate which was more rapid than that usually seen with salicylates. These findings were soon verified by other workers.

Because of the scarcity of cortisone, the effects of adrenocorticotropic hormone (ACTH) prepared from the pituitary gland were promptly tested by many investigators and equally spectacular results were obtained when this was given in doses of 50 to 200 mg. daily. Thorn has estimated that the injection of 4 mg. of ACTH daily stimulates the secretion of adrenal hormones equivalent to 25 mg. of compound E.

Since these initial discoveries, the therapeutic possibilities of ACTH, and to a lesser extent compound E, have been explored in a wide variety of disorders. Most of this work has not been published and in many instances only a few cases have been studied so that it is impossible to evaluate it adequately. In October 1949, at a meeting in Chicago sponsored by The Armour Laboratories, the results of most of the workers in the field were informally discussed and pooled. From the preliminary data presented it is possible to formulate the following general impressions:

1. In allergic reactions such as asthma, hay fever and serum sickness, acute attacks are reported to be relieved promptly but usually recur after a few weeks if the patient is exposed again to the allergin. A severe reaction to penicillin responded in dramatic fashion.

2. In acute rheumatic fever which may represent a tissue hypersensitivity response it is possible that ACTH or cortisone may arrest or terminate the attack and that there may be no further progress or relapse. It is possible that some cases of acute nephritis, where tissue hypersensitivity plays a role, may be benefited. Nephrosis was usually made worse by ACTH because of salt retention, but after discontinuing therapy improvement followed and the course of the disease seemed to be altered. A favorable response has also been observed in a case of Loeffler's syndrome.

3. In more severe and more prolonged disorders of hypersensitivity, such as rheumatoid arthritis, lupus erythematosis and periarteritis nodosa, all symptoms may clear up within a few days but nearly all cases have relapsed after withdrawing treatment.

4. In certain infections—a case of virus pneumonia and one of pneumococcus pneumonia—the fever ceased abruptly but the pulmonary process was not affected and the pneumococcus persisted in the blood stream. A patient with acute tuberculosis who had had persistent fever became afebrile after 2 days, but the disease progressed and cavitation occurred in spite of treatment for 40 days. The tuberculin test may become negative during treatment and becomes positive again after discontinuing it.

5. In certain conditions in which there may be infiltrations of lymphoid tissue, it is possible that ACTH or compound E may cause disappearance of this tissue, but lymphoid leukemia, although improved, has relapsed shortly. The same was true in a case of Hodgkin's disease. Some cases of scleroderma and dermatomyositis are said to be improved.

Many other conditions such as poliomyelitis, muscular dystrophy, myasthenia gravis, parkinsonism and schizophrenia have been treated either without improvement or with unfavorable results.

It is generally agreed that in rheumatic and other diseases which are favorably influenced there is no deficiency of adrenal hormones. One gets the impression that ACTH and compound E in some way alter the tissue hypersensitivity in those disorders in which this is a factor. They do not affect the invading organism or increase the immune responses of the body to the organism. They also cause the disintegration of some lymphoid tissues. The manner in which these reactions is brought about is not yet known. The fibrinogen of the blood, the sedimentation rate and the globulin are decreased. The eosinophil count falls.

Toxic manifestations may occur. If treatment is continued with either ACTH or compound E for a long period, symptoms of Cushing's syndrome including obesity and hyperglycemia may be produced. It is even possible that eventually true diabetes might result. With ACTH it is possible to cause salt and water retention, due to stimulation of the salt-retaining hormones of the adrenal, but this is usually not sufficient to be dangerous unless there is cardiac disease. It is also possible to cause a dangerous loss of potassium. Interestingly enough, ACTH has caused an Addisonian type of pigmentation.

Finally it should be pointed out that the actions of ACTH and compound E are not identical. ACTH causes increased secretion of all types of adrenal hormones—salt-retaining, carbohydrate-regulating and androgenic. Compound E belongs to the carbohydrate-regulating group of hormones. Actually it is probably not secreted by the adrenal, and compound F, which acts the same as E, is probably the hormone produced. The indications for treatment with ACTH and with compound E probably differ in various conditions. From what has been said it is obvious that neither of these drugs is a miraculous cure. They are agents which afford some degree of control over certain body reactions. Further investigation of their action will yield valuable information concerning the nature of certain disease processes. At the present time they are neither available nor desirable for general therapeutic uses but are valuable in the hands of the scientific investigator.

Clinical Problems of the Adrenal Cortex: Deficiency in the Newborn Infant; Tumors and Hyperplasia of Childhood

Dr. William C. Deamer: I will talk briefly on the use of adrenal cortex preparation other than the recent, much publicized, cortisone. The preparations I have in mind are the aqueous or oil extracts of the natural gland cortex and the various desoxycorticosterone acetate preparations which are synthetic. These may find usefulness in situations such as the following:

1. The Waterhouse-Friderichsen syndrome of acute collapse with bilateral hemorrhage into the adrenal glands at birth or in septicemia. 2. Addison's disease, which is especially likely to be associated with the adreno-genital syndrome. 3. Adrenal insufficiency due to severe toxic diphtheria and possibly other severe toxemia-shock situations. 4. Operations on the adrenal gland, in which the opposite gland may be atrophied.

The types of preparations available are: 1. adrenal cortex gland extracts: (a) aqueous (beef), Upjohn, Wilson, Parke-Davis (Eschatin), and Armour. 10 cc. and 50 cc. packages. (b) In sesame oil (hog), Upjohn Lipo-Adrenal Cortex. Expensive. 2. Synthetic desoxycorticosterone acetate preparations: (a) in sesame oil for intramuscular use 1 cc. = 5 mg. Cortate (Schering), Doca (Roche), Percorten (Ciba). (b) Pellets for subcutaneous use: Ciba 125 mg. and Schering 75 mg. Absorption rates quite variable but average 0.35 mg. a day for the 125 mg. pellet and 0.24 mg. a day for the 75 mg. pellet; i.e., 75 mg. pellet lasts about 300 days. (c) Solution in propylene glycol for sublingual use. Schering "Cortate" 1 cc. = 10 mg. (d) Sublingual tablets 5 and 10 mg. Ciba (Linguettes) and Schering.

The aqueous and oil gland extracts are relatively safe to use even in large quantities, are more expensive and supply a wider coverage of adrenal cortex functions than the synthetic preparations. The oil extract is more complete in its coverage than the aqueous extracts. The synthetic preparations lack almost entirely the carbohydrate regulating effect and have such a strong salt-retaining effect that excess dosage must be carefully watched and avoided.

Salt-retaining effect (in order): desoxycorticosterone; aqueous gland extract; lipoadrenal extract.

Carbohydrate regulating effect (in order); lipoadrenal extract; aqueous gland extract; desoxycorticosterone (nil).

In treating a patient in adrenal crisis one should keep in mind the great temporary need for use of the natural gland product, either aqueous or oil-extracted. An adult may need as much as 200 cc. of the aqueous extract in 24 hours. Even such an amount is usually safe as far as its salt and water retaining effects are concerned.

The following plan of treatment is largely that recommended by Thorn* and the amounts are suitable for an adult. Proportionate reductions in dosage should be made for children and infants.

Treatment of Crisis: 1. Adrenalin 0.25 cc. if blood pressure is low. 2. Aqueous extract 5 to 10 cc. intravenously or intramuscularly, followed by 1 to 2 cc. every hour, then every 2 hours, then every 3 hours, and finally every 6 hours over the period of a few days, depending on patient's response. Lipoadrenal extract, intramuscularly, may be used in place of any part of this aqueous dosage (1 cc. equalling roughly 10 cc. of the aqueous extract) and may be given every 6 to 8 hours in place of every 1 to 2 hours. In addition, give: 3. Desoxycorticosterone 2 to 5 mg. in oil intramuscularly (along with the extract mentioned above) followed by 1 to 2 mg. daily depending on hydration, blood pressure, weight gain and other indices of water and salt retention. In addition, one may need: 4. Supportive measures, such as blood plasma (50 to 100 cc.) or human albumin (5 to 10 cc.) in glucose-saline solution intravenously, preferably slowly (containing the aqueous gland extract mentioned above). Penicillin may be indicated prophylactically, but avoid morphine.

Preparation for Adrenal Surgery or Surgery in Patient with Chronic Adrenal Insufficiency: 1. Adrenocorticotrophic hormone 5 to 10 mg. daily for 3 days before operation to activate and enlarge opposite gland if operation is on an adrenal gland. 2. In any case aqueous gland extract 1 to 2 cc. every 4 hours for 24 hours before operation, or to equivalent lipoadrenal extract (i.e., 0.2 to 0.4 cc. every 8 hours). 3. Glucose and saline solution with 5 cc. aqueous gland extract before and after (or during) operation. No morphine sulfate or avertin. Epinephrine as needed for low blood pressure.

Treatment of Chronic Insufficiency: Desoxycorticosterone acetate pellet implanted subcutaneously after patient has been regulated, this to take the place of other medication and of extra sodium chloride, which can be added during periods of diarrhea or of excessive heat, when 1 to 2 gm. of extra salt may be given daily. During periods of severe illness, or gastrointestinal disturbance, adrenal gland extract may also be needed.

The signs of overdosage with desoxycorticosterone are: edema, hypertension, cardiac enlargement, headache and weakness.

In the future new synthetic compounds, the "11-oxy" group, will probably become available and supply the carbohydrate regulating feature now lacking in the desoxycorticosterone group.

Dr. Wilkins (in discussion of Dr. Deamer's talk): There are several points on which Dr. Deamer touched which I would like to repeat for the sake of emphasis.

As Dr. Deamer stated, it is very important in cases of acute adrenal failure to give large amounts of the aqueous extract of adrenal or lipoadrenal in oil and not to depend solely on desoxycorticosterone and salt. Desoxycorticosterone does not support the carbohydrate metabolism and in fact may even precipitate hypoglycemia. After the patient has been tided over an adrenal crisis, if there is a chronic adrenal insufficiency, he may be maintained on salt alone or with desoxycorticosterone. However, in the presence of stress such as an acute infection, treatment with the other adrenal hormones again may be indicated. There is practically no danger from overdosage with aqueous extracts of adrenal in amounts up to 50-11 cc. a day and usually patients are undertreated rather than overtreated because of the expense. Lipoadrenal is more potent and is comparatively innocuous. When desoxycorticosterone and salt are given excessively there is danger from sodium retention and hypopotassemia, and cardiac failure may result.

In infancy and childhood acute adrenal insufficiency may result from the following conditions: (1) In the neonatal period, adrenal hemorrhage due to trauma or hemorrhagic diathesis. (2) With acute infections, especially diphtheria and meningitis due to toxic degeneration and necrosis of the cells of the fascicular zone rather than hemorrhages and gross necrosis such as described by Waterhouse and Friderichsen. Clinically in diphtheria it is necessary to distinguish between the peripheral

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* Thorn, G. W., *The Diagnosis and Treatment of Adrenal Insufficiency*, Springfield, Ill., Charles C Thomas, Publisher, 1949.

circulatory collapse due to adrenal insufficiency and myocardial failure. (3) Adrenal failure following removal of an adrenal cortical tumor. In these cases the function of the contralateral adrenal may have been suppressed by the hypersecretion of the tumor and supportive therapy with adrenal hormones may be required in the postoperative period. (4) The Addisonian-like picture, occurring in some cases of congenital adrenal hyperplasia which Dr. Deamer has just discussed. I would like to call attention to the fact that occasionally the electrolyte changes may be manifested not by the dehydration, weight loss, and gastrointestinal symptoms just described but by the ECG changes of high potassium and heart block and cardiac failure. (5) There are a few cases during childhood of true Addison's disease due to tuberculosis or adrenal atrophy. There may occasionally be a congenital aplasia of the adrenals. (6) Finally, Dr. Jaudon in St. Louis described a number of young infants with dehydration, failure to gain and low serum sodium, all of whom he believed had a transient adrenal insufficiency. I have not encountered this condition and Dr. Deamer tells me that he has not either. I would warn against making such a diagnosis merely on the basis of low sodium. Low serum sodium may be found in some intestinal disorders and in renal abnormalities such as the "salt-losing kidney" described by Thorn.

Discussion

Dr. Morton Zall, Los Angeles: Please elaborate on the lesser indications for thyroid.

Chairman Reilly: I mentioned eczema, obesity and nephrosis. Now let it be clearly understood that when thyroid is used in those diseases, if we do get any good effect it isn't a proof positive that the patient lacked thyroid substance in his body. It may be that he does not have a hormone or endocrinal deficiency at all but that the thyroid medication in these diseases may act as a general tonic, stimulating effect or some metabolic effect. For instance, in nephrosis, the thyroid substance as a rule isn't very successful but occasionally it is a good diuretic. In order to get an effect in nephrosis you have, as a rule, to give tremendous doses of thyroid substance. Perhaps it isn't as well absorbed in the bowel. Eczema patients are helped at times by thyroid substance.

Dr. Hugh C. Thompson, Tuscon, Ariz.: In children of 1 or 2 years in whom growth has come to a standstill and the bone age is 6 to 12 months behind the average, but who have a normal cholesterol and no classic signs of cretinism, is the administration of thyroid indicated?

Chairman Reilly: My answer to that would be that it is very possible normally to have a retardation of the epiphysial development of 6 to 12 months at that age of 1 to 2 years and that again is a laboratory test. We use the laboratory tests particularly in mild hypothyroidism where, for instance, you do not recognize much myxedema. We feel, in general, that a bone age can be plus or minus 6 months to 18 months at any age so that 1 to 2 years of age chronologically is hard to check properly by bone age. Now, however, the therapeutic tests with thyroid substance is worth while but by itself will not be pathognomonic proof that a patient is a cretin.

Dr. Robert P. Rogers, Greenwich, Conn.: It was stated that intrabdominal undescended testicle is 50 times more likely to have malignant changes. Is there evidence against this assumption?

Chairman Reilly: I am afraid I misled you. I said, "The undescended testicle is no more subject to malignancy than the descended one according to Dr. William Carroll's extensive investigations of that problem in San Francisco." He based that on taking some several hundred cases of tumor of the testicle of which they had a very good record and showed that malignancy didn't have any greater frequency in undescended testes. It is true that the testicle in the abdomen is more likely to develop malignancy.

Dr. F. H. Redewill, Jr., Whittier, Calif.: Does blood iodine and blood cholesterol and BMR or any new laboratory procedures have definite value in quantitatively evaluating thyroid dosage?

Dr. Wilkins: Sometimes a high serum cholesterol gives a clue to diagnosis or helps confirm it but the cholesterol may not be elevated in young cretins. The blood iodine is of less value in hypothyroidism than hyperthyroidism. The level is not closely correlated with the degree of deficiency.

Chairman Reilly: It is usually hard to do a BMR in children. You may get a normal today, 10% less tomorrow and after the child gets used to the procedure it may be consistently 15 or 20 minus. You might have thought that, with his normal BMR on first test, it indicated only a small dose. This is a mistake. I do not think laboratory work can help you in evaluating quantitatively. Blood iodine is of less value in hypothyroidism than in hyperthyroidism.

Dr. Sidney Rose, Los Angeles: Is hormone therapy indicated in hirsutism of older girls and, if so, what is the best procedure?

Dr. Wilkins: I know of no satisfactory endocrine treatment for hirsutism. Certainly in the doses in which it can be given safely estrogen does not inhibit the secretion of androgen or antagonize its effect on sexual hair. In fact, in patients with ovarian agenesis, estrogen increases the 17-ketosteroid excretion and the sexual hair. I would be opposed to giving estrogen to a hairy girl during adolescence because it may seriously interfere with the normal pituitary-ovarian mechanism during this important period of adjustment.

Dr. Irving B. Richter, Chicago: Have you had any success with endocrine therapy in the symmetrically understatured child?

Chairman Reilly: In the first place, this could be the so-called primordial dwarfism. He is simply a genetic dwarf constitutionally made up that way; he may not lack growth hormone because his epiphysial development is normal as a rule. He develops dwarfism genetically, matures normally and nothing can be given for extra growth. On the other hand, if he is a hypopituitary dwarf, the bone age is delayed but he may be quite symmetric, yet treatment is not very satisfactory. The only thing available now from a practical standpoint, as Dr. Deamer pointed out a few years ago, is male hormone. Dr. Lawson Wilkins has recently been working with the newer growth hormones of Evans and Li.

Dr. Wilkins: During the past year the Armour Laboratories asked 6 to 7 different groups of investigators to study in humans the effects of the Evans-Li growth hormone which they had prepared in concentrated and fairly purified form. Likewise Dr. Kinsell of San Francisco experimented with an electrophoretically pure preparation of Li and Evans. None of the investigators was able to demonstrate any favorable effects on protein anabolism or growth. In fact the patients showed loss of appetite and weight, negative nitrogen balances and certain toxic effects. These results did not seem to be due to contaminating hormones or to allergic reactions. It is not known whether there is a species difference so that the beef or sheep pituitary is effective in the rat or dog but not in the human or whether there is some toxic contaminant. As yet no pituitary growth hormone has been proved to be effective in the human.

Dr. Paul M. Hamilton, San Marino, Calif.: What is your feeling about thyroid in obesity?

Chairman Reilly: Thyroid deficient patients rarely become very obese. I think we will have to agree that excess obesity is not due to much thyroid lack or primary hypothyroidism. You can give thyroid substance in obesity for the following reason: it stimulates metabolism and thereby some weight might be lost but do not rely on the thyroid extract to reduce weight greatly. I said earlier that these people who are obese and are receiving thyroid extract may take a tremendous dose sometime before they seem to get toxic symptoms; they don't need it. They may not absorb much out of their bowel or the end organs are not sensitive enough to react because there isn't primarily a deficiency in the thyroid substance.

Dr. R. Hatfield, Salina, Kansas: Please discuss the problem of mongolism and thyroid extract.

Chairman Reilly: Mongols are not hypothyroids primarily. On the other hand, mongols are liable to have hypothyroidism also in the same frequency as the rest of the childhood population. I give thyroid extract to mongols because the family feels that thyroid is going to help them. I administer it with the advice that I do not expect that it is going to help and it will not hurt but I want to prove it to the satisfaction of the family. Some mongols will temporarily improve. They reach a certain plateau, the amount of the improvement is minimal and the family are then perfectly willing to stop the thyroid extract. On the other hand, I have seen mongols taking thyroid for years and it does not seem to hurt them.

Dr. S. E. Pasette, Los Angeles: Do you prefer blood iodine to cholesterol for clinical use?

Chairman Reilly: I would not prefer cholesterol to blood iodine for practice. The blood iodine determination is a very difficult one to do and the technician has to be accustomed to doing it. It takes 10 cc. of blood and a good deal of technical equipment; the amount of the normal is 4 to 8 gamma per cent, such a small amount that technical error easily occurs. However, if the technical procedure is very reliable, I am inclined to favor blood iodine over cholesterol.

Dr. Henry Silvers, San Francisco: What are the expected results with gonadotrophin in the unilateral versus the bilateral undescended testes?

Chairman Reilly: If the undescended one is held fast by anatomic defect, gonadotrophin will not help; if it is partly mobile, hormone may help to bring it down part or all way. The patient will get his greatest help from his own gonadotrophin at puberty; surgery may still be necessary. Hormone should be given pre- and postoperatively.

Dr. Harry Medovy, Winnipeg, Manitoba, Canada: Do you believe in giving small doses of thyroid

to adolescent girls on the basis of a possible thyroid deficiency, not necessarily demonstrated clinically?

Chairman Reilly: If there is definite deficiency I would give small doses of thyroid along with 1 or 2 drops of Lugol's solution and watch for improvement or worsening. I have occasionally seen tall, asthenic adolescent girls with nervousness and a low BMR who improve on thyroid. Prolonged and irregular menstruation is corrected by thyroid in some cases.

Dr. Paul M. Hamilton, San Marino, Calif.: Does testosterone tend to creat premature epiphysial closure?

Dr. Wilkins: I do not think that with testosterone therapy there is an undue risk of epiphysial fusion, although this formerly was considered a danger. Androgen causes an acceleration of linear growth, muscular and osseous development followed by gradual epiphysial closure similar to that which occurs normally during adolescence. Now the effects of estrogen may be different. Estrogen may actually inhibit growth of the epiphysial cartilage and lead to rapid fusion. Cases have been brought to my attention in which estrogen has apparently caused small undeveloped epiphysial centers to unite with the shafts of the bone. Some endocrinologists have even advocated giving estrogen to adolescent girls who show a tendency to grow excessively tall. I would be seriously opposed to this because I believe that the administration of estrogen may interfere with the delicately balanced pituitary ovarian mechanism which is undergoing transitional development at this time.

Dr. Deamer: What do you think is the reason that these individuals show an advancement of bone age over other age factors and even the wider separation of your bone age in your chart from height age after given testosterone?

Dr. Wilkins: Your point is well taken that in cases of male sexual precocity, especially when due to hyperadrenocorticism, the bone age may be advanced to a far greater extent than the height age. In such cases the very excessive secretion of androgen is probably responsible. I am speaking of therapeutic dosages of androgen which are probably more in the range of the secretion occurring in early or mid-adolescence.

Dr. William J. Ball, Minot, N.D.: Could someone discuss idiopathic precocious puberty as described by Novak?

Dr. Wilkins: I regret that in this symposium therapy has been discussed without presenting the background of the underlying endocrine mechanism or the differential diagnosis of the various syndromes. Probably 80 or 90% of all cases of sexual precocity are of the so-called "constitutional" or "idiopathic" type. In these cases there is apparently a normal pituitary-gonadal mechanism and the gonadotropic activities of the pituitary merely have begun at an early age for some unknown reason. In some cases there is a hereditary tendency to precocious puberty; in others there is not. It is necessary to distinguish the idiopathic cases from those in which the pituitary-gonadotropic mechanism has been initiated by some lesion in the hypothalamus or brain.

Pediatrics

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SPECIAL SECTIONS

NEWS AND ANNOUNCEMENTS

Dr. Aims C. McGuinness, director of the Children's Hospital, has been named dean of the University of Pennsylvania's Graduate School of Medicine. He will assume his new duties on the first of the year. He succeeds Dr. William S. Parker, who resigned recently.

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The following diplomates were certified by the American Board of Pediatrics, Inc.:

CHICAGO—OCT. 13, 14 AND 15, 1950

Anderson, Arnold Severen, 412 Excelsior Ave., Hopkins, Minn.
Baker, Charles R., 3450 W. 43rd St., Los Angeles
Bongiovanni, Alfred M., 1208 Belfield Ave., Drexel Hill, Pa.
Branson, Vernon Lee, 112 S. 6th, Beatrice, Neb.
Canmann, Mark F., 2 N. Sheridan Rd., Highland Park, Ill.
Concepcion, Leon L., Tarlac, P.I.
Corn, Henry H., 532 Des Moines Bldg., Des Moines, Ia.
Cotsirilos, Peter J., 6001 Cermak, Cicero, Ill.
Crook, William Grant, 110 W. Baltimore, Jackson, Tenn.
Cunningham, Ernest Samuel, Jr., 623 S. Henderson, Ft. Worth, Tex.
Dalton, Arthur Markham, 2434 Sylvania Ave., Toledo
Dammers, Warren Robert, 575 Lincoln Ave., Winnetka, Ill.
Doezema, Edward Rhiner, 1419 Waverly Dr., Kalamazoo, Mich.
Drake, Miles Edward, Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia
Dubow, Emanuel, 36 Gramercy Park, New York City
Gilger, William Grant, II, 2024 Schaaf Rd., Cleveland
Gilles, Helen Martin, 747 Massachusetts Ave., Lawrence, Kan.
Greenwald, Richard M., 67-35 Yellowstone Blvd., Forest Hills, L.I., N.Y.
Hart, Walter Moore, 105 W. Cheves St., Florence, S.C.
Holland, Mark Peter, 27 S. Catawissa St., Mahoney City, Pa.
Hughes, Gerald E., 1107 Bryant Bldg., 1102 Grand, Kansas City, Mo.
Kernodle, George Wallace, 305 W. Front St., Burlington, N.C.
Kinder, James Absolom, Jr., 826 Themis St., Cape Girardeau, Mo.
King, Nancy Burfoot, 3 W. Williamsburg Rd., Sandston, Va.
Koerner, Kenneth A., 7803 Clayton Rd., St. Louis
Lawson, James B., 500 Downing, Denver
Leininger, C. Ray, Albert Bldg., 1010 B St., San Rafael, Calif.
Levy, Harold B., 1727 Line Ave., Shreveport, La.
Lindsay, Douglas Twichell, Public Welfare Board of North Dakota, Bismarck, N.D.

MacKenzie, Ellen Pickard, 33 Fifth St., Gretna, La.
Maggio, George Anthony, 419 Roseville Ave., Newark
Morris, Robert A., 2003 Meridian St., Anderson, Ind.
Nelson, George W., 2814 9th Ave., N., Billings, Mont.
Parmelee, Arthur Hawley, Jr., 909 Via De La Paz, Pacific Palisades, Calif.
Pierson, Paul Starrett, 1005 W. Green Tree Rd., Milwaukee
Rosenfeld, George Bernard, Children's Hospital, 219 Bryant St., Buffalo
Rosenzweig, Joseph Leon, 126 Hawthorne St., Hot Springs, Ark.
Scherling, Sidney S., 3333 Alabama, Minneapolis
Shaffer, Jerome Daniels, 1200 N. Walker, Oklahoma City
Silverman, Louis B., Grand Forks Clinic, Grand Forks, N.D.
Steinberg, Richard Mitten, 5133 Washington St., Downer's Grove, Ill.
Stephens, George K., 106 E. 13th St., Ada, Okla.
Sterner, John Alwin, 633 Medical Dental Bldg., Seattle
Tanner, William A., 1922 University Ave., Madison, Wis.
Thompson, Ben F., Jr., 3170 Florida St., Baton Rouge, La.
Tuuri, Arthur L., Mott Foundation, Children's Clinic, Flint, Mich.
Wake, Douglas L., 1406 Woodsboro Dr., Royal Oak, Mich.
Williamson, Lee, 1052 N. 5th, Abilene, Texas.
Wissmath, Frank Sum, 35 N. Central Ave., Clayton, Mo.
Womack, Harry Hall, Jr., 1216 Pennsylvania Ave., Fort Worth, Texas

Written examinations under local monitors will be held on Friday, Jan. 19, 1951 from 2:00 to 4:00 P.M. This is the only written examination which will be given during 1951. The next oral examination will be in New Orleans, March 2, 3 and 4, 1951.

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Dr. Leona Baumgartner has returned to her post as Assistant Commissioner of the New York City Department of Health, having been on leave of absence since June 1949. During this period she served as Associate Chief of the Children's Bureau, Federal Security Agency. She will continue to serve the Children's Bureau as special advisor to the Office of the Chief.

* * *

Dr. Lewis K. Sweet, former chief medical officer in pediatrics at Gallinger Hospital, died of a heart attack at his home in Falls Church, Va.

Dr. Sweet recently had resigned to accept a research position with the National Institute of Health in Bethesda, Md. He was a foremost authority on poliomyelitis and for several years had directed Gallinger's extensive polio services.

BOOK REVIEWS

VISION, ITS DEVELOPMENT IN INFANT AND CHILD, Arnold Gesell, M.D., Frances L. Ilg, M.D., and Glenna Bullis, assisted by Vivienne Ilg, O.D., and G. N. Getman, O.D., New York, Paul B. Hoeber, Inc., 1949, $6.50, 352 pp., 179 illustrations.

Those familiar with the previous writings of Dr. Gesell and his associates will undoubtedly greet this newest work with justifiable anticipation. Gesell views the human eye as virtually a vestibule of the brain and vision as pre-eminent in the sensory-motor construction of the human action system. The human eye develops just as the body develops and the development of the former plays an important role in the development of the latter. The book is another of Gesell's combinations of carefully recorded and intelligently reported observations documented with photographs of the subjects themselves.

The present volume is based upon a concept of developmental morphology, according to the authors, and is in 3 sections. The first deals with the concept of the total action system and with both the ontogeny and phylogeny of vision. The study is of the total child of whom vision is part and parcel but nevertheless only a part. He is a growing child. Studies at each age level of development help to focus attention upon the changes from 1 level to the next and thus growth becomes measurable.

The second section deals more specifically with the developmental morphology of visual behavior patterns. The authors find that vision does not develop in a symmetric proportionate manner but the complex which is vision undergoes many transformations. The chapter on the developmental aspects of amentia, cerebral palsy and total blindness is particularly good and of both interest and value to every pediatrician with patients suffering from any of the 3 conditions. Case studies provide acid-sharp illustrations of the points made by the authors.

The third section briefly sets forth the implications of a developmental approach to technics of appraisal and supervision. A developmental approach is said to broaden the scope and the goal of visual hygiene. The authors believe that this volume is, in a sense, a preface to a Developmental Optics which they define as being concerned with the ontogenesis and the organization of visual functions in their dynamic relation to the total action system.

This reviewer happens to be an ophthalmologist and to have had the opportunity of working with infants and children a great deal of the time. There are certain parts of the book which are directly in the field of ophthalmology and with which a large number of ophthalmologists are going to take serious issue, particularly the subject of dynamic retinoscopy as it is handled.

The statement is made that ". . . visual maladaptations, not to say defects, are mounting alarmingly in the years from five to ten. The increase of myopia among children and adults has serious portent." No evidence is cited for this statement and it is open to serious doubt. True enough, our diagnostic methods are improving and visual testing among school children in their earliest school years is gaining widespread popularity. For this reason, more children with defects are being found but this is not sufficient evidence to say that defects are increasing. Over 25 years ago, it was found that 60% of the population in this country was far-sighted and the rest near-sighted. A study of over 1,200 school children just completed revealed that 59.3% were far-sighted aand the rest near-sighted. This hardly appears to be an increase in near-sightedness.

Gesell is at his best when analyzing his own careful observations such as the following, written about the infant aged 32 weeks: "He is not so self-contained. His reactions are less forthright and his face often wears a questioning, half-confused expression. He shows a greater sensitiveness in new situations and he needs more time to adjust to them. (This is not a favorable age for a visit to the doctor's office.) Even familiar environment fatigues the child more readily, because he has a deepening awareness of himself in relation to the environment. Such sensitiveness combined with assimilativeness is part of the process of growth, and it involves his visual functions which are developing in close correlation with his social attitudes."

He states that he accepts the ideas of Chavasse about reflexes as they pertain to vision and then makes such statements as the following (in speaking of a 5 year old child): ". . . in the visual

examination, herefore, he is able to report and to *maintain* a phoria at near distances."* One does not maintain a reflex and the 2 thoughts are directly contradictory.

The greatest disagreement comes with the use of retinoscopy. The fact that the retinoscopic reflex is at times bright and at times dim may indeed mean a shift in accommodation or it may mean a slight shift in the visual axis—more likely the latter from the description given of the technic. It is well nigh impossible to see how any examiner could align himself along the primary axis of the eye and yet have the child looking at pictures; it seems more likely that a secondary axis was used.

To attribute changes in the color of the retinoscopic reflexes to changes in the mental process is going a great deal farther than the reviewer cares to go. It is too bad that these same changes were not sought under cycloplegia if, as is implied, they are the result of mental processes. It would have been a very simple method of eliminating a tremendous variable.

The authors write of phoria testing when the patient is ' interpreting around the plane of regard" and also when the patient is "not interpreting around the plane of regard." Presumably the former expression means that the child is looking at the fixation object used in the phoria tests. If this is correct, it means that at other times the child was not watching the object and, if this is true, then whatever was measured was not phoria, but something else.

The reviewer is forced to be very critical of the conclusions drawn from tests of prism vergence with the apparent variation and fluctuation found at various ages. It has certainly not been his experience that muscle balance studies are significantly variable between the ages of 3 and 10. Tests of muscle balance in children have been shown to have a high reliability and also they have been shown not to vary significantly with age. An experienced examiner can tell immediately when his examinations of muscle balance in any of its phases is becoming unreliable through loss of attention by the child due to fatigue, distraction, etc. Further persistence with the examination merely yields weird and highly variable findings, similar perhaps to watching a driverless car running aimlessly about over a vast desert. One may report its wanderings in great detail but certainly can draw no conclusions about the absent driver. When attention lapses, the same situation maintains with respect to observations on the binocular neuromuscular mechanism.

The book has some extremely valuable observations on the relationship of vision to the development of the organism and probably valid conclusions are drawn, for they are well documented. On the other hand, the reported observations on retinoscopy and all the binocular tests of muscle balance are of interest but it is believed that any attempts to draw conclusions as has been done are perhaps dangerous and certainly unwarranted.

CHILDREN IN CONFLICT, Madeleine L. Rambert, New York, International Universities Press, Inc., 1949, $3.32, 214 pp.

Psychiatric treatment based on Freudian psychoanalytic principles is being applied increasingly with children. Many times parents do not understand what is entailed in such treatment, particularly if it is more or less orthodox psychoanalysis. *Children in Conflict* has been written for parents in order that they might understand better how a psychoanalyst works with children. Choosing from case material, the author illustrates many of the facets of psychoanalytic theory. At the end of the book is a brief glossary of technical terms which are rapidly coming into the everyday language of most medical practitioners. Such terms as ambivalence, cathartic, identification, inhibition, narcissism, repression, sublimation and super ego no longer are restricted to psychiatric terminology.

The author is a Frenchwoman and describes her manner of working with children; her methods are not those to which most American therapists would subscribe. For example, she has made it the rule that before psychotherapy is started the child submits to extensive examinations as to his physical health, the degree of his intelligence and the character of his social adjustment. Some of our ablest therapists in this country would feel that although physical examinations and psychometric studies are indicated frequently, these must be selectively chosen for the individual case.

Although parents may well gain some idea of what psychoanalytic treatment with children as practiced by Mlle. Rambert amounts to, it is questionable whether the average parent and teacher and pediatrician will be able to understand and, therefore, to use much of the symbolic material presented in this book. It is recommended more for professional persons working in the field of psychology, psychiatry and social work than it is for parents or pediatricians.

* Reviewer's italics.

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